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## Trajectory of Neurocognitive Functioning in Psychotic Disorders

Zanelli, Jolanta

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# **Trajectory of Neurocognitive Functioning in Psychotic Disorders**

**Jolanta Zanelli**

Thesis submitted for the degree of Doctor of Philosophy

Institute of Psychiatry

King's College London

University of London

## *Dedication*

For my late parents, Janina and Władysław.

Thank you for everything

## **Abstract**

Although cognitive deficits are recognised as a core feature of schizophrenia, their trajectory over the course of the illness is still debated. The primary objectives of this thesis were: (i) to determine the neuropsychological profile at the first episode of psychosis (Chapter 3); (ii) to examine gender differences in the profile of neuropsychological performance (Chapter 4) and (iii) to determine if cognitive abilities decline, remain static or modestly improve throughout the course of psychotic illness (Chapter 5).

The first (baseline) analyses form part the AESOP (Aetiology and Ethnicity in Schizophrenia and Other Psychoses) study, a population based, case-control study of first-episode psychosis recruited over a three-year period between September 1997 to August 2000 in London, Bristol and Nottingham. The second analyses (follow-up, where I followed 108 patients and 103 healthy controls) also form part the AESOP study, conducted 6 to 10 years afterwards but only in London and Nottingham.

In this thesis I found that early in the course of psychotic illness cognitive deficits are present in all psychotic disorders, but are most severe and pervasive in schizophrenia and least pervasive in bipolar. There was strong evidence for gender differences in neuropsychological performance but these differences were disorder specific. Gender related factors appear to moderate the severity of cognitive deficits in bipolar/mania and depressive psychosis patients. Future schizophrenia patients had an early static developmental impairment on measures relying on knowledge acquisition (verbal IQ). This static deficit increases in size starting in late adolescence or early adult life. There was also an increase in deficit on memory functions. Future bipolar patients had normal or slightly above normal knowledge acquisition scores (verbal IQ) which started to deteriorate starting in early adult life. Thus, both schizophrenia and bipolar/mania patients show dynamic changes in general and specific cognitive functions which start early in childhood and continue across the life span. Both depressive psychosis and other psychotic disorders show different age related changes than schizophrenia or bipolar/mania. However because of small sample size and lack of studies examining the premorbid period therefore it is difficult to provide a life course model.

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## **Personal contribution to the investigation**

I joined the AESOP study in 2003 and I have participated in all aspects of the follow-up study, as well as assisting in cleaning-up and reliability-testing of baseline data.

Specifically, my involvement includes:

### **Recruitment**

I contributed to the original of subject-tracing strategies and contact procedures. I administrated subject tracing for the team as well as tracing my own assigned caseload which involved making contact with cases or healthy controls; approaching participants for recruitment and explanation of follow-up to participants.

### **Neuropsychology battery evaluation**

I assessed: 45-50 patients and similar number of controls; helped with participant tracing for the follow-up. I have been responsible for arranging interviews (as research coordinator for the AESOP study). I took a prominent role in analysis and organisation of the baseline data enabling other members of the AESOP team to conduct their own baseline investigation. I have been responsible for scoring and coding of all raw data for purposes of data entry. In addition I have been photocopying medical notes. Also I was involved in coordinating follow-up neuropsychology data from healthy controls for the 10 year follow-up in Nottingham centre. The follow up data in this thesis was analysed by myself with the collaboration of Sven Sandin from the Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden

## **Database**

I was responsible for the design, instigation and maintenance of the data for the whole follow-up investigation e.g., Neuropsychology, NSS, MPA, Life Chart, Forensics; preparing for data entry from the follow-up and cleaning up some data from the baseline study.

## **Administrative aspects of the AESOP team - main co-ordinator**

I was responsible for booking rooms and transport; meeting and greeting subjects on the arrival; looking after all financial aspects including subject payments; preparing packs with all assessments. I often chaperoned other researcher on home/loP visits when conducting other clinical interviews. I independently constructed and maintained the AESOP shared drive. I was responsible for writing minutes from the meetings

# Chapter 1 An introduction to psychosis

## 1.1 Introduction

The term psychosis derives from the Greek words '**psyche**' (the soul; the spirit; the mind) and '**osis**' (denoting a process or condition, esp. a pathological state). It refers to mental states where there is some loss of contact with reality and where there are disturbances to the normal process of thought perception. In 1845 Feuchterleben, coined the word 'psychosis' in his book entitled "The Principles of Medical Psychology" where he proposed psychosis as a term for severe mental disorders (Beer, 1995). This concept has since undergone a number of refinements. One early definitional adjustment was the suggestion that psychosis represented a disease process (Ban, 1976). In modern usage, the term psychosis refers broadly to severe psychiatric disorders, including schizophrenia, and some organic and affective disorders. Numerous criteria have been proposed to achieve a more precise definition, but there problems with all of them. In the fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000) it is emphasised that definitions of the term psychosis have never received universal acceptance. In the DSM-IV's broadest definition, psychotic symptoms consist of hallucinations, delusions, disorganised speech and grossly disorganised or catatonic behaviour. This more expansive symptom list is similar to those detailed in the World Health Organisation's Classification of Mental and Behavioural Disorders (World Health Organization., 1992)

### 1.1.1 The functional and organic psychoses

A fundamental distinction was made between the 'organic' and the 'functional' psychoses (Beer, 1995) during the late nineteenth century. In organic psychoses, the emergence of symptoms arises from a clear pathology of the brain. Organic psychoses may occur as a result of cerebral hypoxia and brain lesions, metabolic and endocrine disorders, vascular abnormalities, infections and nutritional deficiencies. Organic mental disorders can be due to a general medical condition or to a brain disease such as Dementia of the Alzheimer's Type (DAT) or temporal lobe epilepsy, or to a psychoactive substance such as amphetamines or cannabis. By contrast in the functional psychoses, mental disturbances arise in the absence of any gross pathological changes to the brain or body. Primary functional psychotic disorders such as schizophrenia and affective

disorders do not have a clearly identified physical basis. In the present study, the research is focused on those disorders which are usually regarded to be functional psychoses.

### 1.1.2 The symptoms of psychosis

#### Positive and negative symptoms

There is a general agreement that people suffering from psychosis may experience a collection of symptoms, which may be grouped as either positive or negative symptoms. Positive symptoms include: hallucinations delusions; disorganised speech or thinking and disorders of behaviour. They indicate the presence of mental activity not normally experienced. **Table 1.1** provides the summary of the primary positive symptoms of psychosis listed in DSM-IV and ICD-10(American Psychiatric Association, 2000, World Health Organization, 1992).

**Table1.1 The positive symptoms of psychosis as defined by DSM-IV and ICD-10**

<b>Hallucinations</b>	auditory, visual, olfactory, tactile
<b>Delusions (of)</b>	reference, persecution, nihilism, grandiosity, control, thought possession
<b>Disorganised speech</b>	stream of thought, flight of ideas, loosening of associations
<b>Disorders of behaviour</b>	gross excitement/overactivity
<b>Motor abnormalities</b>	catatonia, gross psychomotor retardation

*Delusions* are false beliefs that are firmly held on inadequate grounds; are not affected by rational argument or evidence to the contrary; furthermore it is not a conventional belief that the person might be expected to hold given her educational, cultural and religious background. Several types of delusions are recognised, either by the characteristics or the theme of the delusion. *Hallucinations* are perceptions experienced in the absence of an external stimulus to the corresponding sense organ. It differs from an illusion in being experienced as originating in the outside world (or sometimes within the person's body) but not within the mind (e.g. mental imagery). A hallucination can be in the mind, with an illusion there is a stimulus which is misinterpreted. *Disorganised speech* is normally inferred by examining abnormalities in speech. *Disorders of behaviour or motor abnormalities* comprise a marked increase in the normal levels of



activity, characterised by hyperactivity, or a marked decrease in activity, characterised by catatonia, or very slowed or fixed movements.

Other symptoms associated with psychotic disorders include negative symptoms such as restricted emotional expression (flat affect), sparse language output (alogia), poor initiation and persistence of goal-directed behaviours (avolition), and inability to feel pleasure (anhedonia) (American Psychiatric Association, 2000). Negative symptoms are difficult to evaluate because they are non-specific, and may be caused by a variety of other factors e.g. medication side effects or mood-disorder (Skrabalo, 1999). They can appear more benign than positive symptoms as they are less distressing to the sufferer who may not even notice them but they are thought to predict a poor outcome. Although negative symptoms are an integral aspect of schizophrenia, neither the DSM-IV nor the ICD-10 explicitly defines negative symptoms as psychotic. Andreasen however, has argued that negative symptoms should be considered a fundamental aspect of psychotic pathology (Andreasen and Flaum, 1991).

## 1.2 The classification of the functional psychoses

### 1.2.1 Schizophrenia

Schizophrenia is a severe psychotic disorder and one of the most common of the severe mental illnesses. Traditionally it was thought that it affects up to one percent of the world population at some point in their life (Jablensky, 2000, Jablensky *et al.*, 1992). Using narrow definitions such as DSM-IV (American Psychiatric Association, 2000), it has an average lifetime prevalence of 0.7% (Saha *et al.*, 2005), and primarily affects adults, being rare in children and becoming gradually more common during adolescence, with the peak age of onset in the early twenties in males, and three or four years later in females (Saha *et al.*, 2005). Females show a later second peak around the time of the menopause (Saha *et al.*, 2005).

Emil Kraepelin carried out work towards the end of the nineteenth century that led to the description of the illness (Kraepelin, 1896). His dichotomy of the functional psychotic conditions, *dementia praecox* and *manic-depressive insanity* into separate disease entities was a landmark in the development of the schizophrenia concept. *Dementia praecox* was a progressive illness that often started in adolescence and followed a downhill course, possibly caused by organic changes to the brain. *Manic-depressive insanity* was a more treatable disorder, with periods of full recovery between episodes of the illness. The *dementia praecox* notion was disputed by Bleuler (Bleuler, 1950). He replaced this term with 'schizophrenia' (meaning split or fragmented mind). The definitions in use today follow Kraepelin's dichotomy and use a syndromic diagnosis based largely on the work of Kurt Schneider (1887-1967), who proposed that certain 'first-rank' symptoms were more reliable (but not necessarily essential) determinants of schizophrenia (Schneider and Hamilton, 1959). These symptoms - third person auditory hallucinations, thought interference, passivity and delusional perceptions – along with persistent delusions, catatonia, and negative symptoms, form the basis of the diagnostic criteria in ICD-10 (World Health Organization., 1992) and DSM-IV (American Psychiatric Association, 2000). However, the conceptualization of the 'first-rank' symptoms has not solved the puzzle regarding the underlying aetio-pathology of the illness. One contemporary view of schizophrenia is one of a heterogeneous group of disorders (Hill *et al.*, 1997). In this respect it is of note that the ICD-10 and DSM-IV (American Psychiatric Association, 2000, World Health Organization., 1994) recognise several sub-types of

schizophrenia including those described as 'paranoid', 'hebephrenic', 'catatonic', 'residual', 'simple', deficit syndrome' and 'undifferentiated'.

### **1.2.2 The affective psychosis (bipolar disorder and depressive psychoses)**

Kraepelin's dichotomy of the functional psychoses was subject to further elaboration when discrete entities within the class of *manic-depressive insanity* were proposed. In its original formulation, the term manic-depressive insanity included patients who suffered from depression only and patients who manifested both 'poles' of affect (mania and depression) at different times. Leonhard (1957) was the first author to separate depression by polarity. He advocated a division of 'bipolar' and 'monopolar' disorders based on the nature of the recurrent episodes. A unipolar (depression only) – bipolar (depression and mania) distinction went into the DSM as the formal diagnostic criteria for affective disorders (Leonhard and Beckmann, 1999).

#### Bipolar disorder

Bipolar disorder has been described as a 'continuum of phenotypes, ranging from a pattern of mild depression and brief hypomania to one of severe rapid cycling or predominantly mania with psychotic features' (Muller-Oerlinghausen *et al.*, 2002). The presence of psychosis is not a requirement for a diagnosis of bipolar disorder. However, psychotic symptoms often occur in both the manic and depressive phases of bipolar disorder (McElroy *et al.*, 1996). Specific sub-categories are listed to distinguish bipolar disorder with or without psychotic symptoms in both the ICD-10 and DSM-IV. Bipolar disorder affects about 1 adult in 100 (National Advisory Mental Health Council, 1993; the prevalence in males and females is the same. Men appear to have an earlier onset than women with an average age of onset (in the United Kingdom) of 22 years and 27 years, respectively (Kennedy *et al.*, 2005).

Patients with bipolar illness cycle through episodes of mania, depression and periods of euthymia (normal mood during periods of remission), and demonstrate a dramatic fluctuations in energy, social behaviour, mood and cognitive functioning. On some occasions, the disturbance consists of mood elevation, disorganised speech, hallucinations, delusions (usually grandiose), increased

energy, increased activity and irritability. This is known as a manic phase. Other episodes of disturbance which often follow a period of emotional euphoria and manic behaviour include a lowering of mood, marked reduction in activity and decreased energy. This is referred to as a depressive phase. For the diagnosis of bipolar disorder (with psychotic features) it is a requirement in both DSM-IV and ICD-10 (American Psychiatric Association, 2000, World Health Organization, 1992) that patients have experienced at least one episode of depression and at least one episode of mania.

### Depressive psychosis

Depressive psychosis is an older term for what is now referred to in DSM-IV (American Psychiatric Association, 2000) as a "major depressive episode, severe, with psychotic features," and in ICD-10 (World Health Organization., 1992) as a "severe depressive episode with psychotic symptoms." This disorder includes symptoms of both depression and psychosis in an individual without an underlying diagnosis of a psychotic disorder. In a major depressive episode with psychotic features, the individual reports or exhibits false beliefs (delusions) and/or hears or sees things that aren't there (usually auditory but sometimes visual hallucinations). The delusions or hallucinations usually refer to depressive themes (mood-congruent psychotic features), such as the belief that one is responsible for the death of a loved one or that one is being punished because of a moral transgression. Hallucinations are usually temporary and may involve voices that berate the individual for perceived wrongs. Occasionally, the content of the delusions or hallucinations has no apparent relationship to depressive themes (mood-incongruent psychotic features) and may include delusions that one is being persecuted or that others can control one's thoughts. In general, mood-incongruent psychotic features are associated with a poorer prognosis than mood-congruent psychotic features. However, patients with severe depression will not necessarily develop psychotic symptoms (Elliott *et al.*, 1996). It has been argued that psychotic depression is more than a simple manifestation of severe depression (Dubovsky, 1994). Approximately 10% to 25% of females and 5% to 12% of males are at a lifetime risk for developing a depressive psychosis, with only a small percentage of those exhibiting psychotic features. As in bipolar disorder, men appear to have an earlier onset than women with an average age of onset (in the United Kingdom) of 22 years and 27 years, respectively (Kennedy *et al.*, 2005).

### **1.2.3 Schizoaffective disorder**

Schizoaffective disorder is included in both the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) criteria and the International Classification of Diseases, Tenth Revision (ICD-10) (World Health Organization, 1992) coding. It is a perplexing mental illness that has both features of schizophrenia, including hallucinations, delusions, and distorted thinking, and features of a mood disorder, such as depression or mania. The coupling of symptoms from these divergent spectrums makes diagnosing and treating patients who are schizoaffective difficult.

The diagnosis is made when the patient has features of both schizophrenia and a mood disorder. Unfortunately, it is often difficult to determine whether a patient has two separate illnesses (schizophrenia or a mood disorder), a combination of illnesses (schizophrenia with a mood disorder), or perhaps even a distinct and separate illness apart from schizophrenia or a mood disorder (Kane, 2010).

### **1.2.4 Other psychosis**

In this category the disorders are conditions in which psychotic symptoms are present but they do not fulfil the criteria to make a formal diagnosis of schizophrenia, bipolar disorder, depressive psychosis or schizoaffective disorder. In the present study, the diagnostic grouping of other psychosis included persistent delusional disorders, acute and transient psychotic disorders, other nonorganic psychotic disorders, and unspecified nonorganic psychosis (ICD-10) (World Health Organization, 1992).

## **1.3 Aetiology of psychosis**

The aetiology of psychosis is not yet fully understood although both genetic and environmental factors have been implicated.

### **1.3.1 Genetic factors**

Genetic susceptibility appears to be the most important influence in psychosis. Three lines of enquiry: family, twin and adoption studies have demonstrated that first degree relatives of an affected individual have 8-10 times the risk of the corresponding disorder in the general population. Most of the variance in risk for each disorder is genetic, twin studies revealing heritability for schizophrenia and bipolar disorder of around 80% or more (Cardno and Gottesman, 2000, McGuffin *et al.*, 2003) with largely unknown environmental factors also being involved. Given their high heritability and the difficulties inherent in direct physiological and pathological studies of living human brain, the identification of specific risk loci offers researchers one of the best chances of understanding pathogenesis.

### **1.3.2 Brain structure**

A large number of imaging studies have shown that schizophrenia and psychotic bipolar disorder are associated with distinct grey matter deficits but anatomically coincident white matter abnormalities (McDonald *et al.*, 2005, Meyer-Lindenberg, 2010). Individuals with schizophrenia have distributed grey matter deficit predominantly involving the fronto-temporal neocortex, medial temporal lobe, insula, thalamus and cerebellum, whereas those with bipolar disorder have much less significant regions of grey matter abnormality. Both groups have anatomically overlapping white matter deficits in regions normally occupied by major longitudinal and interhemispheric tracts. In chronic schizophrenia, more extensive volume reductions are observed in the cortex, particularly in medial and left dorsolateral prefrontal cortex, but also in the left superior temporal gyrus (Ellison-Wright *et al.*, 2008). However in first-episode schizophrenia volume increases are restricted to parts of the putamen (Ellison-Wright *et al.*, 2008). These increases are not heritable (Goldman *et al.*, 2008) and are probably a consequence of a number of environmental factors including antipsychotic drug action.

### 1.3.3 Neurochemistry

Several neurotransmitters have been implicated in the development of schizophrenic symptoms including dopamine, serotonin and glutamate. Most recent theories on dopamine activity suggest a deregulation of dopamine neurotransmission (Howes and Kapur, 2009, Sunahara *et al.*, 1993). They are based on the observation that dopamine agonists can induce psychotic symptoms (Ellison, 1994). The investigation of neurochemical abnormalities in the psychosis have indicated that the neurotransmitter serotonin and glutamate play an active role in their development (Howes *et al.*, 2012, Javitt and Coyle, 2004).

### 1.3.4 Environmental factors

A number of studies have shown that obstetric complications (pregnancy and birth complications, abnormal foetal growth) are associated with increased rates of schizophrenia and other psychosis (Cannon *et al.*, 2002b, Dalman *et al.*, 1999). Whether obstetric complications initiate disruption in the brain development or are the consequence of pre-existing neural abnormalities remain unresolved (McGrath and Murray, 1995). Other possible early environmental insults include exposure to viruses influenza during pregnancy (e.g. (Rantakallio *et al.*, 1997, Wright *et al.*, 1995) and malnutrition (Susser *et al.*, 1998).

Drug abuse, such as amphetamine, is among other environmental risk factors occurring later in life, known to be able to trigger psychotic like symptoms (Chen *et al.*, 2003). There is increased evidence suggesting modulating effects of cannabis on time of onset, severity and outcome of schizophrenia. Epidemiological studies have shown that early substance use (i.e. cannabis) among individuals who are at genetic risk may increase the likelihood of developing psychotic symptoms in adulthood. Caspi *et al.* provided evidence that those who carry the ValVal allele of the COMT gene and consume marijuana at an early age are at greater risk for developing psychotic symptoms later in life (Caspi *et al.*, 2005). Furthermore, Smesny *et al.*, found that the observed effects of cannabis on lipid metabolism in schizophrenia support the notion of gene x environment interaction (Smesny *et al.*, 2007). Furthermore, Henquet *et al.*, studies showed that

use of cannabis is associated with almost twice the risk for schizophrenia (Henquet *et al.*, 2005a, Henquet *et al.*, 2005b).



## **Chapter 2 Neuropsychology**

### **2.1 Basic concept in neuropsychology**

Neuropsychology has been defined as the 'study of the relationship between brain function and behaviour. Neuropsychological assessment (i.e. administration of neuropsychological tests, test-score analysis and interpretation of data) is a method of examining the brain by studying its behavioural product. Since the subject matter of neuropsychological assessment is behaviour, it relies on many of the same techniques, assumptions, and theories as does psychological assessment. The distinctive character of neuropsychological assessment lies in a conceptual frame of reference that takes brain function as its point of departure. Interpretation of performance data involves the determination of the presence or absence of a marked discrepancy between any two or more scores (Lezak, 1995, Silverstein, 1982). Thus, a corollary assumption in neuropsychology is that the analysis of marked discrepancies between levels at which a person performs different cognitive functions provides a window into the structure of normal cognitive systems that is, by the assumption that the results generated by this research activity will provide insights into the structure of cognitive mechanisms-and that it will ultimately provide important constraints for theories of the neural basis for cognitive functioning. Once the nature of neuropsychological impairment has been established, data from successive neuropsychological examinations repeated at regular intervals can provide reliable indications of whether the underlying condition is changing, and if so, how rapidly and in what ways. Once the nature of neuropsychological impairment has been established,

The multidimensional and complex nature of most neuropsychological tests that, implicitly or explicitly, involve a number of different functions, makes it impossible to identify the specific deficits that underlie any given lowered test score without a systematic search for each component function that is involved in the neuropsychological test under examination (Keefe, 1995). Also an inherent problem germane to individual neuropsychological functioning is that performance on many tests is usually influenced by several cognitive processes, despite the fact that an individual test may be differentially weighted to assess only one particular domain (Heinrichs and Zakzanis, 1998). An example of this is on the Trail Making Test (for a description of the task, see chapter 3). Evidence obtained from frontal lobe damaged patients, who were

impaired on this task suggests that the Trail Making Test –part A may reflect visual search whereas the part B may tap the executive domain assessing mental flexibility and set shifting. However, to complete this task successfully, a degree of attentional effort as well as motor and perceptual speed is required (Heinrichs and Zakzanis, 1998). The scores obtained therefore do not index a single cognitive function.

Dating back to the work of Spearman (Spearman, 1961), a distinction has been made between general and specific cognitive abilities. Two widely used indices of generalised neurocognitive performance have been applied in schizophrenia research: general measures of intelligence quotient, or IQ, and composite scores or profiles derived from test batteries comprising multiple neuropsychological tests. Although both provide a measure of an individual's overall cognitive functioning, the results of these assessments often do not overlap to a substantial degree. Neuropsychological test batteries typically focus on assessment of multiple cognitive abilities, such as memory, executive functions, and attention, and these include a strong component of novelty of testing requirements. IQ tests, on the other hand, have a lesser emphasis on specific abilities and novelty and greater emphasis on the assessment of crystallized abilities (Bratti and Bilder, 2006).

## 2.2 Neuropsychology and psychosis

Neuropsychological impairments are core features of schizophrenia and are related to functional status and other aspects of illness (Green, 1996, Heinrichs and Zakzanis, 1998) and although they are common in schizophrenia, they are not specific to this illness. They are evident also in the subjects with affective psychoses (Gilvarry *et al.*, 2001, Goldberg *et al.*, 1993, Gruzelier *et al.*, 1988, McGrath *et al.*, 1997, Sweeney *et al.*, 2000, Zubieta *et al.*, 2001) schizoaffective disorder (Evans *et al.*, 1999, Gooding and Tallent, 2002, Miller *et al.*, 1996) and other forms of functional psychosis (Mitrushina *et al.*, 1996, Zanelli *et al.*, 2010). However, it appears that neuropsychological impairments are more severe in schizophrenia. In several studies, patients with schizophrenia have been shown to be more impaired in a range of cognitive tests than patients with bipolar disorder and other functional psychotic conditions (Gilvarry *et al.*, 2001, Goldberg, 1999, Mitrushina *et al.*, 1996, Seidman *et al.*, 2002).

Neuropsychological abnormalities are evident many years before the overt expression of any psychotic symptoms (Aylward *et al.*, 1984, David *et al.*, 1997, Davidson *et al.*, 1999, Hoff *et al.*, 1999, Jones *et al.*, 1994, Reichenberg *et al.*, 2002). These cognitive symptoms are considerably developed at the time of the first psychiatric contact (Bilder *et al.*, 2000, Saykin *et al.*, 1994). First episode psychotic patients appear to have deficits in neuropsychological functioning that are similar to those seen in patients with chronic illness, although patients with poor outcome show some signs of deterioration in intellectual functioning in later life (Harvey *et al.*, 1999a). Cognitive deficits are persistent and are observed at similar levels of severity even when symptoms have remitted (Addington and Addington, 1993, Barbarotto *et al.*, 2001, Martinez-Aran *et al.*, 2002, Silverstein *et al.*, 1998). Similar, yet milder, abnormal neuropsychological performance has been observed in the non-psychotic relatives of schizophrenia patients (Cannon *et al.*, 2000, Faraone *et al.*, 1996, Goldberg *et al.*, 1995, Goldberg *et al.*, 1990, Keefe *et al.*, 1994) and in patients with schizophrenia-spectrum conditions (Bergman *et al.*, 1998, Mitropoulou *et al.*, 2002, Moriarty *et al.*, 2003, Roitman *et al.*, 2000, Trestman *et al.*, 1995).

Neurocognitive deficits do not respond markedly to treatment with atypical or typical antipsychotic medications despite the fact that these medications reduce the psychotic symptoms of the

disorder (Blyler and Gold, 2000). In addition, it has been demonstrated that abnormal neuropsychological functioning predicts a variety of aspects of poor functional outcome, including community function and skill learning in schizophrenia (Green, 1996, Green *et al.*, 2000).

## **2.3 Methodological issues in the application of neuropsychology in psychosis**

While there are a number of methodological issues pertinent to neuropsychological research, several factors of great importance need to be taken into consideration.

### **2.3.1 Matching**

The issue of matching patients and healthy control participants on a number of background variables in order to control for confounding influences is an area of ongoing controversy (Goldstein, 1996a). On the one hand, association between performance on neuropsychological measures and level of education is almost unquestionable (Heaton *et al.*, 1991, Heaton *et al.*, 1996). On the other hand, educational level is itself confounded by several variables including presence of psychotic disorder.

Various premorbid indicators are used to match across, or controlled for and covaried through statistical means: age, socioeconomic status, education are a few examples of variables used. The rationale behind using premorbid indicators is that these variables may affect performance on cognitive tasks.

The most common indicator of premorbid ability and hence matching criterion used in the literature is the National Adult Reading Test (NART) (Nelson and Willison, 1991). However, matching on this variable also does not escape confounding difficulties. When used in conditions such as schizophrenia, education achievement is usually curtailed at a young age which would obviously affect outcome. On the other hand, a similar concern with bipolar disorder seems unfounded, as bipolar patients are more likely to complete higher education (Torrey, 1999).

### **2.3.2 Medication**

The influence of medication has long been recognised as possibly disadvantageous to neuropsychological performance. In addition, psychotic patients are often treated with a cocktail of drugs at any given time. These can include antipsychotics, antidepressants, sedatives, and anticholinergics. All of these drugs affect multiple aspects of cognition (Lader, 1999, Minzenberg *et al.*, 2004, Pachet and Wisniewski, 2003, Sharma *et al.*, 1999). For example, antipsychotic treatment seems to improve some cognitive functions and to have a deteriorated effect on others (Rund *et al.*, 1997, Rund *et al.*, 1996, Spohn and Strauss, 1989). Anticholinergic drugs have been shown to impair some cognitive functions, such as verbal recall, independently of any autochthonous process of deterioration (Spohn and Strauss, 1989).

On the whole, most studies employed to assess the effect of typical antipsychotics on cognition indicate a limited normalisation of some neuropsychological functions. For example, several literature reviews suggest a modest improvement in attention (Heaton and Crowley, 1981, Spohn and Strauss, 1989) and visuomotor function (Cassens *et al.*, 1990). However, the results from a meta-analysis by Guilera *et al.*, suggest that compared to typical antipsychotics, atypical drugs produce a slight improvement in the global cognitive index, and several cognitive domains show a slight improvement in the neuropsychological performance of patients (Guilera *et al.*, 2009).

Finally, in longitudinal studies, in which a great number of cognitive and neuropsychological functions have been assessed and the doses of antipsychotic and anticholinergic medication might have changed dramatically or been discontinued, it is a complex task to evaluate how the findings are affected by medication.

### **2.3.3 Clinical symptoms**

Whether neuropsychological impairment merely reflects a transient state that passes with the alleviation of symptoms has been debated for many years. On balance, different cognitive domains may be affected differentially, depending on several variables such as first episode, chronicity, co-morbid substance abuse, illness severity (in terms of number of episodes and

degree of inter-episode recovery) and the polarity of the episode. Studies on first episode versus chronic patients, on clinically stabilised populations and on children at high risk of developing the disease suggest that cognitive impairment represent an integral part of the disease process (Goldberg *et al.*, 1993, Hoff *et al.*, 1992). Nonetheless, well-designed longitudinal studies evaluating changes in clinical state and the effect produced on neuropsychological performance are scarce. The inconsistency of many cognitive and psychosocial results reported may be partly due to these differences in patients' clinical features.

## **2.4 Aims of the study**

The objective of the study is to investigate baseline and trajectory of neurocognitive functioning in psychotic disorders. In the next chapter (Chapter 3) I will report the outcome of neuropsychological performance in the baseline study. Neuropsychological performance was compared between four major diagnostic groups with their first episode of psychotic disorders: schizophrenia, bipolar/manic disorder, depressive psychotic disorder, and other psychotic disorders. To examine specificity, the performance of each diagnostic group was compared with that of controls, followed by direct comparison of non-schizophrenia psychotic disorders with schizophrenia. Finally, the affective-psychotic groups are also compared.

Based on the literature reviewed in Chapter 2.2, I tested the hypothesis that:

Neuropsychological impairment will be evident across psychotic disorders but will be more severe in schizophrenia compared with affective psychosis (Reichenberg et al., 2009).

In Chapter 4 I will investigate whether there are gender differences in the profile of neuropsychological performance in patients with first episode of psychosis. Because of the conflicting results in previous research, which examined cognition particularly in schizophrenia, no a priori hypothesis regarding gender differences in neuropsychological performance was made. The thesis describes methodology and presents the findings of the investigation with the aim of developing a greater understanding of the gender differences particularly in affective disorders.

Finally in the Chapter 5 I will examine the following three questions:

- 1) What is the trajectory of the cognitive impairment seen in psychosis after the first psychotic episode?
- 2) Do all neuropsychological deficits follow the same trajectory?
- 3) Do different psychotic disorders present the same trajectory of cognitive functioning?



## **Chapter 3 Neuropsychological profile in patients with first episode of psychosis**

### **3.1 Introduction**

Neuropsychological deficit is a key clinical feature of schizophrenia, and has also been found in association with other psychotic disorders (Bilder *et al.*, 2000, Green and Nuechterlein, 1999, Hill *et al.*, 2004) (Gold and Green, 2005). However, only a small number of studies have compared cognitive function between bipolar/ manic patients, schizophrenia, depressive psychosis, other psychotic disorder patients and healthy volunteers.

The neuropsychological profile is typically characterised by prominent specific deficits, in memory and learning, executive functions, attention and processing speed, which are evident on a background of a generalized cognitive deficit (Palmer *et al.*, 1997, Saykin *et al.*, 1991). The majority of previous neuropsychological studies evaluating patients with first onset of psychosis compared to healthy controls have shown impaired performance in psychotic patients in several cognitive domains, including memory, executive functioning, attention, language, motor skills, and spatial ability (Addington *et al.*, 2003, Bilder *et al.*, 2000, Keefe *et al.*, 2006, Mohamed *et al.*, 1999). These investigations have led to the proposition that schizophrenia should be seen as a disorder associated with generalized cognitive deficits (Bilder *et al.*, 2000, Dickinson *et al.*, 2004). However, there is no universal agreement on the latter notion, and there have been studies that highlighted executive functioning (Hutton *et al.*, 1998, Riley *et al.*, 2000) or verbal memory (Censits *et al.*, 1997, Hoff *et al.*, 1999, Saykin *et al.*, 1991, Saykin *et al.*, 1994) as the central feature of the cognitive impairment associated with schizophrenia.

Although cognitive dysfunction is more severe in schizophrenia, patients with other functional psychotic disorders also demonstrate a disruption to normal cognitive processing. This is evident in the affective psychoses (Brown *et al.*, 1994, Elliott *et al.*, 1996, Gilvarry *et al.*, 2001, Zubieta *et al.*, 2001) schizoaffective disorder (Evans *et al.*, 1999, Gooding and Tallent, 2002) and other forms of functional psychosis (Mitrushina *et al.*, 1996).

Comparisons of the profile and magnitude of the neuropsychological deficits of patients with schizophrenia with those of patients with other psychotic disorders might have important implications for understanding the pathogenesis of these disorders, and for nosological models of psychotic disorders.

Many reports have suggested that patients with other psychotic disorders also demonstrate a disruption of normal neuropsychological performance (Evans *et al.*, 1999, Gilvarry *et al.*, 2001, Gooding and Tallent, 2002). The majority of research has focused on the comparison of schizophrenia with bipolar disorder. While some studies show that patients with schizophrenia manifest more severe neuropsychological impairments (Goldberg *et al.*, 1993, Schretlen *et al.*, 2007, Seidman *et al.*, 2002) others did not detect differences in severity of impairments between bipolar psychosis and schizophrenia (Albus *et al.*, 1996, Hoff *et al.*, 1990). Furthermore, studies comparing neuropsychological performance between schizophrenia and psychotic depressive disorder are rare (Fleming *et al.*, 2004, Jeste *et al.*, 1996, Reichenberg *et al.*, 2009).

A major limitation of most previous studies is that they used clinical, rather than population based samples. Clinical samples include patient series, not complete populations of everyone with the disorder or symptoms. The clinical sample will be a subset of the population sample and can be biased by help seeking, referral bias and severity. The prognosis will tend to be worse and comorbidity more common. As a result, it is difficult to generalise from studies using clinical samples to everyone with the symptoms or disorder. Previous studies of first-episode patients were well done and sometimes had large samples. However, studies varied considerably in terms of the sources for case ascertainment (e.g., university clinics, referral centres or in-patient samples), and the age, duration of illness and medication status of patients. Moreover, while some studies used specific diagnostic groups, others examined heterogeneous groups. These issues further hinder the interpretation of this research, the validity of comparisons and the degree to which it can be generalised. On the other hand a population based sample will include milder variants or heterogeneous conditions with similar phenotypes hence there are also concerns with regard to generalising from a population based sample to a clinical one.

### **3.1.1 Aims and objectives**

Neuropsychological performance is compared between four major diagnostic groups with their first episode of psychotic disorders: schizophrenia, bipolar/manic disorder, depressive psychotic disorder, and other psychotic disorders. To examine specificity, the performance of each diagnostic group is compared with that of controls, followed by direct comparison of non-schizophrenia psychotic disorders with schizophrenia. Finally, the affective-psychotic groups are also compared. Three features of my investigation are especially important. This investigation represents the largest epidemiological cohort of first-episode psychosis patients with neuropsychological data. Second, a large control sample was epidemiologically ascertained, enabling detailed and careful comparisons with patients. Finally, both patient and control samples are ethnically diverse thus increasing the potential to generalise of my results.

## **3.2 Materials and methods**

### **3.2.1 Study design**

The baseline analyses form part the AESOP (Aetiology and Ethnicity in Schizophrenia and Other Psychoses) study, a population based, case-control study of first-episode psychosis recruited over a three-year period between September 1997 to August 2000 in London, Bristol and Nottingham. Ethical approval for the AESOP study was granted by each region's appropriate Research Committee and each participant gave written informed consent after receiving a complete description of the study.

### **3.2.2 The sample**

#### Cases

The study (baseline) identified all cases aged 16-64 years with a first episode of psychosis (F10-F29 and F30-F33 in ICD-10) who presented to specialist mental health services in tightly defined catchment areas in South-East London, Nottingham (between September 1997 and August 2000) and in Bristol over a nine-month period (September 1997 to May 1998). The South London catchment area comprised the former Bethlem and Maudsley NHS Trust areas served by the Maudsley Hospital and the former South Western Hospital. Those catchment areas represent a large area of South London encompassing the boroughs of Lambeth, Southwark and Croydon. Nottingham has well-circumscribed area served by a single provider of mental health services (Nottingham Healthcare NHS Trust). Finally, the Bristol area comprised the well-defined catchment area of the Avon and Wiltshire Mental Health Partnership NHS trust.

All potential cases that made contact with psychiatric services for the first time (including adult community mental health teams, inpatient units, forensic services, learning disability services, adolescent mental health services, and drug and alcohol units) were screened. All potential points of contact with secondary psychiatric services (both in-patient and out-patient services) were regularly surveyed by phone or personal contact.

Identified participants were screened for the presence of psychotic symptoms with the 'Screening Schedule for Psychosis' based on the Psychosis Screening Questionnaire (Bebbington and Nayani, 1995). This questionnaire explores the presence of a broad range of psychotic experiences. Participants positive for the Psychosis Screening Questionnaire and who gave their written consent were then assessed with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.0) (World Health Organization., 1994). The SCAN is an instrument designed to enable the formulation of psychiatric diagnoses (Janca *et al.*, 1994). Using the data obtained with the SCAN, consensus diagnoses were agreed for each participant. Those participants who did not meet the diagnostic criteria of a functional psychotic disorder according to the ICD-10 (1992) criteria were excluded from the study.

The patients identified were then entered into further assessments if they satisfied following inclusion criteria:

- Age 16-64 years.
- Resident within the study area.
- Absence of moderate or severe learning disability as defined by ICD10 (World Health Organisation, 1992b).
- Presence of a functional psychotic illness (ICD10 F10-19, excluding coding F1x.0 for Acute intoxication; F20-29 and F30-39, psychotic coding) (World Health Organisation, 1992b).
- No previous contact with health services for psychosis.

The exclusion criteria were:

- Transient psychotic symptoms due to acute intoxication (as defined by ICD-10), following the administration of alcohol or other psychoactive substance.
- Presence of a disease of the central nervous system.
- History of head trauma resulting in loss of consciousness for over an hour.
- An IQ of less than 50.

- Poor fluency in English language (cases were required to be native speakers of English or to have migrated to the UK by age 11).

All assessments were conducted as soon as possible after initial presentation, as soon as participants were deemed able to sustain the interview by the responsible clinician.

### Healthy controls

The study included a random sample of healthy controls with no past or present psychotic disorder, who were recruited using a sampling method that matched cases and controls by area of residence.

Healthy individuals aged 16-64 were recruited using local press advertisements, household visits, and snowball sampling (i.e. the controls were asked to provide the names of other potential volunteers). The control sample also included a small number of Institute of Psychiatry and Maudsley Hospital staff. Participants identified were screened for the presence of psychotic symptoms with the Psychosis Screening Questionnaire (Bebbington and Nayani, 1995). Participants who rated positive for psychosis during this interview were also assessed by researchers trained in the SCAN to establish the presence or otherwise of a psychotic history. Only subjects negative for psychotic symptoms were entered into further assessment.

Exclusion criteria for healthy individuals were:

- Evidence of any psychotic disorder (past or present).
- Presence of disease of the central nervous system.
- History of head trauma resulting in loss of consciousness for over one hour.
- An IQ of less than 50.
- Poor fluency in English language (healthy individuals were required to be native speakers of English or to have migrated to the UK by age 11).

Participants who met the inclusion criteria were supplied with an information sheet describing the study and were reassured of the confidentiality of any information provided to the researchers. Only volunteers who gave their written consent were included in the investigation.

**Figure 3.1 The Analytic Cohort – baseline study**

<b>AESOP Baseline Cohort</b>		
	<b>Cases</b>	<b>Controls</b>
<b>Baseline cohort</b>	<b>592</b>	<b>412</b>
<b>Non-Participants (refused or could not be contacted or spoke no English)</b>	202 ← ↓	↓
<b>Consented</b>	<b>390</b>	<b>412</b>
<b>Incomplete or no neuropsychological testing</b>	145 ← ↓	↓ → 148
<b>Complete Neuropsychological Testing</b>	<b>245</b>	<b>264</b>
<b>Excluded:</b> <ul style="list-style-type: none"> <li>• Poor English speakers – Likely to affect neuropsychological tests</li> <li>• Missing data on more than three neuropsychological measures</li> <li>• Diagnosis of schizoaffective disorder – Too small for meaningful analysis</li> </ul>	58 ← ↓	↓ → 87
<b>Remaining in Analytic Cohort</b>	<b>187</b>	<b>177</b>

The derivation of the sample included in the analysis reported here is presented in **Figure 3.1**. The analytic cohort comprised of 187 subjects who had a consensus ICD-10 (World Health Organization, 1992) diagnosis of schizophrenia (N=65; F20), bipolar/mania (N=37; F30.2, F31.2, F31.5), depressive psychosis (N=39; F32.3; F33.3), or other psychotic disorders (N=46; including F22 Persistent delusional disorders, F23 Acute and transient psychotic disorders, F28 Other non

organic psychotic disorders and F29 Unspecified nonorganic psychosis), and 177 controls. For all cases and controls there was complete interview data as well as a) IQ measurements on the National Adult Reading Test (NART) (Nelson and Willison, 1991), and a short form of the Wechsler Adult Intelligence Scale – Revised (WAIS-R) (Wechsler, 1981); and b) a neuropsychological battery (see below). Cases and controls were required to be native speakers of English or to have migrated to the UK by age 11. The latter requirement ensured that each participant had a good command of English as a non-native language as they would have completed at least their secondary education in the UK, thus minimising the effect of linguistic or cultural biases on the performance of a multi-ethnic sample. In accordance with previous studies (Reichenberg *et al.*, 2009) cases or controls with missing data on more than three neuropsychological measures were excluded.

### **3.2.3 Diagnostic assessment and symptom data**

Clinical data were collected using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing *et al.*, 1990, World Health Organization., 1994). The SCAN incorporates the Present State Examination Version 10, which is used to elicit symptom-related data at the time of presentation. Ratings on the SCAN are based on clinical interview, case note review and information from informants (e.g. health professionals, close relatives). Researchers were trained in the SCAN interview on a World-Health-Organization (WHO) approved course and established pre-study reliability using independent rating of videotaped interviews. Principal investigators in each center produced independent diagnostic ratings on 20 case vignettes chosen at random from the entire sample. The kappa scores ranged from 1.0 for psychosis as a category to between 0.6 and 0.8 for individual diagnoses. ICD-10 diagnoses were determined using the SCAN data on the basis of consensus meetings involving one of the principal investigators and other members of the research team.

Symptom ratings: Symptom ratings were calculated according to the SCAN's Item Group Checklist (IGC) algorithm. The IGC combines scores from several SCAN items specific to a particular group of symptoms. For example: The IGC item, *Special features of depressed mood* includes feeling of loss of feeling, unremitting depression, morning depression, preoccupation with



catastrophe, pathological guilt, guilty ideas of reference, loss of self esteem and dulled perception. Scores for individual item groups range from 0 (absent) to a maximum of 2 depending on the frequency and severity of symptoms. Following a recent meta analysis (Demjaha *et al.*, 2009) individual item groups were aggregated into three symptoms dimensions: **Negative Symptoms** (Flat and incongruous affect, Poverty of speech, Motor retardation and Catatonic behaviour, and Nonverbal communication); **Reality Distortion** (Bizarre delusions and interpretations, Delusions of reference, Delusions of persecution, Experience of disordered form of thoughts, Nonspecific auditory hallucinations, and Non-affective auditory hallucinations), and **Depression** (Depressed mood, Depressive delusions and hallucinations, and Special features of depressed mood).

### 3.2.4 Neuropsychological assessment

Sixteen neuropsychological measures were selected to assess six domains: (1) Learning and Memory (verbal and visual); (2) Executive functions and working memory; (3) Attention, concentration and mental speed; (4) Language; (5) Visual constructual/perceptual abilities, and (6) WAIS-R verbal intelligence.

#### 3.2.4.1 Learning and memory domain

Learning and memory were assessed using trials 1 through 5 (learning), trial 6 (immediate recall), and trial 7 (delayed recall), respectively, of the Rey Auditory Verbal Learning Test (RAVLT), and the Visual Reproduction sub test of the Wechsler Memory Scale - Revised (WMS-R) (Wechsler, 1987).

##### Rey Auditory Verbal Learning Test (RAVLT)

The RAVLT ((Spreen and Strauss, 1991) p149-157) is useful in evaluating verbal learning and memory, including proactive inhibition, retroactive inhibition, retention, encoding versus retrieval, and subjective organization. The examiner reads list A of 15 words aloud at the rate of one per second to the subject who then has to repeat as many words as possible from the list - in any

order. This procedure is then repeated for trials A2-A5. After trial 5, the examiner presents a second list B of 15 words to the subject who then has to recall as many words as possible from word list B (this is trial B1). The subject is then asked to recall as many words as possible from word list A (without hearing word list A read out again) (this is trial A6). After a 20-minute delay period, filled with other activity, the subject is asked to recall the words from list A (again, without hearing word list A read out again) (this is trial A7).

### Visual Reproduction

Nonverbal memory was assessed using the Visual Reproduction sub-test of the Wechsler Memory Scale Revised (WMS-R) (Wechsler, 1987). This is a visual recall test. It requires the subject to reproduce from memory simple geometric designs that were shown briefly (10 seconds). There are three cards with designs adopted from the Army Performance tests and Binet. Scoring was calculated in accordance with Wechsler's guidelines (Wechsler, 1945, 1974). The largest obtainable score is 14.

### **3.2.4.2 Executive functions and working memory domain**

Executive functions and working memory were evaluated using the Trail Making Test - part B, Letter-Number Span, and Sets AB and B of Raven's Coloured Progressive Matrices (CPM).

### Trail Making test (part B)

This test measures attention, visuospatial tracking, and perceptual motor speed (Reitan, 1979, Reitan, 1985, Reitan, 1958, Reitan, 1992). Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In part B, the circles include both numbers (1 – 13) and letters (A – L); as in part A, the subject draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The subject should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time the subject as he or she connects the "trail." If the subject makes an error, it is pointed out immediately and allowed the subject to correct it. Errors affect the

subject's score only in that the correction of errors is included in the completion time for the task. It is considered by the author to be unnecessary and probably unkind to continue the test beyond 4-5 minutes.

### Letter-Number Span

The Letter-Number Span (Gold *et al.*, 1997) is a task that is designed to measure verbal working memory. Subjects hear a list of numbers and letters and are instructed to repeat the numbers first, from smallest to biggest, then the letters in alphabetical order. The test has six levels with four trials at each level, for a total of 24 trials. The first level begins with a two-item string and each level increases the item-string by one, ending with a seven-item string. For example, a subject would hear "w7t4," and the correct answer is "47tw." Following a series of practice trials, the test involves 4 trials at each string length, beginning with 2-item strings (such as "m3") and proceeding up to 7-item strings (such as "uc7g4qls") for a total of 24 items. Testing continues until the subject fails all four trials at a single level. The total number of correct responses (of 24 possible) is used for the analyses. The test is terminated when a subject fails all 4 trials at any 1 string length.

### Sets AB and B of Raven's Coloured Progressive Matrices (CPM)

Ravens Coloured Progressive Matrices (Spreeen and Strauss, 1991) is a pattern based test relatively free of any language component that provides a 'culture fair' estimate of cognitive functioning. It is a task of intellectual ability sensitive to fluid intelligence. The CPM Sets A, AB, B is arranged to assess mental development up to the stage when a person is sufficiently able to reason by analogy to adopt this way of thinking as a consistent method of inference. This apparently decisive stage in intellectual maturation appears to be one of the earliest to decline as the result of organic dysfunction. This test contains sets A and B from the standard matrices, with a further set of 12 items inserted between the two, as set AB. Most items are presented on a coloured background to make the test visually stimulating for participants. However the very last few items in set B are presented as black-on-white. In each test item, the subject is asked to

identify the missing element that completes a pattern. Many patterns are presented in the form of a 4x4, 3x3, or 2x2 matrix, giving the test its name.

#### **3.2.4.3 Attention, concentration and processing speed domain**

Attention, concentration and processing speed were measured using Trail Making - part A, and the WAIS-R Digit Symbol subtest.

##### Trail Making test (part A)

Trail Making Test (part A) Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the subject should draw lines to connect the numbers in ascending order.

##### WAIS-R Digit Symbol subtest

WAIS-R Digit Symbol subtest from the Wechsler adult intelligence scale-revised (Wechsler, 1981). The Digit Symbol task is used to assess psychomotor speed and involves auditory attention. It consists of (e.g. nine) digit-symbol pairs (e.g. 1/-, 2/ $\perp$  ... 7/ $\wedge$ , 8/X, 9/=) followed by a list of digits. Under each digit the participant should write down the corresponding symbol as fast as possible. Before beginning the test, participant gets to practice by completing the sample section (i.e. first 7 boxes on the worksheet). The number of correct symbols within the allowed time (90 sec) is measured.

#### **3.2.4.4 Language domain**

Language was evaluated using verbal fluency: the Category (Semantic) Fluency (categories 'body parts', 'fruits' and 'animals'), and Letter Fluency (letters F, A, S).

### Verbal fluency

The Controlled Oral Word Association Test (Yeudall *et al.*, 1987) was used to language. Category (Semantic) Fluency test entails the generation of words from a given category ('body parts', 'fruits' and 'animals') within a pre-set time of 30 seconds. Letter Fluency (letters F, A, S) task. In this task participants are asked to generate as many words as possible that begin with a designated letter (F, A, S). This task is believed to emphasize the phonemic characteristics of words rather than the meaning of words.

### **3.2.4.5 Visual-spatial perception and organisation domain**

Visual-Spatial Perception and Organisation were assessed using set A of Raven's Coloured Progressive Matrices and the WAIS-R Block Design.

### Set A of Raven's Coloured Progressive Matrices

Please see above

### WAIS-R Block Design subtest

WAIS-R Block Design subtest from the Wechsler adult intelligence scale-revised (Wechsler, 1981). The Block Design task is a measure of spatial ability and psychomotor speed. Participants have to visually analyse abstract figures from a series of printed two dimensional geometric patterns and then replicate the designs using a set of two-coloured cubes.

### **3.2.4.6 WAIS-R verbal intelligence domain**

WAIS-R Verbal Intelligence was assessed by the WAIS-R Vocabulary and Comprehension sub tests. For a detailed description of measures see references: (Gold *et al.*, 1997, Lezak *et al.*, 2004, Spreen and Strauss, 1991, Spreen and Strauss, 1998).

### The WAIS-R Vocabulary subtest

The WAIS-R Vocabulary subtest from the Wechsler adult intelligence scale-revised (Wechsler, 1981). The Vocabulary test examines the individual's knowledge of word meanings and the ability to express those meanings verbally. Participants attempt to define a series of words presented to them both visually and orally.

### The WAIS-R Comprehension subtest

The WAIS-R Comprehension subtest from the Wechsler adult intelligence scale-revised (Wechsler, 1981). The Comprehension test assesses common sense reasoning and the ability to deal with abstract social conventions, rules and expressions (e.g., "What does *kill two birds with one stone* metaphorically mean?"). It comprises a series of orally presented questions that require the individual to solve everyday problems or show understanding of social rules and concepts.

## **3.2.5 General intelligence**

### **3.2.5.1 Premorbid intelligence**

Premorbid intelligence was estimated using the National Adult Reading Test (NART) (Nelson and Willison, 1991). The National Adult Reading Test is widely used to provide an estimate of premorbid intelligence. The NART is simple to administer and to perform. The person taking the test is asked to look at and pronounce, aloud, 50 words. None of the words fully follows the usual rules of English grapheme-phoneme correspondence or stress (e.g., ache, thyme, topiary). Therefore, if a person has not encountered the NART's words previously, applying normal rules of pronunciation will not lead to the correct answer. Scoring for this test is based on the number of errors made. The correlation between the NART generated IQ score and the WAIS-R IQ is very high (Crawford *et al.*, 1991, Nelson and Willison, 1991). Discrepancy between the premorbid IQ from the NART and current IQ obtained on testing gives an estimate of intellectual deterioration.

### **3.2.5.2 Full-scale IQ**

Full-scale IQ was derived from the WAIS-R (Wechsler, 1981) subtests in the neuropsychological testing battery. The WAIS-R is one of the most extensively used tests of intellectual abilities. It is aimed at individuals aged 16 and older and has been standardised according to a range of adult bands. This study used a shortened version of the WAIS-R (Lezak *et al.*, 2004, Spreen and Strauss, 1998). Short forms of the WAIS-R have been shown to produce an accurate estimate of full scale IQ (e.g. (Roth *et al.*, 1984, Silverstein, 1982). This study included four subtests of the main WAIS-R battery: Vocabulary, Comprehension, Block Design and Digit Symbol. Combinations of these subtests also provide estimates for verbal IQ and performance IQ.

### **3.2.6 Creating norms for neuropsychological tests.**

Neuropsychological tests often do not have good population norms that one can standardise test against and if they do these tests are not co-standardised (each test has norms from an entirely different control sample). To overcome this limitation, a regression based approach was used to create normative standards for the neuropsychological tests. Age, gender, ethnicity and education were regressed on each of the neuropsychological measures in the healthy sample. Then, scores were adjusted on the basis of these regression results and standard (i.e., Z) scores were created. The regression corrected scores were also inspected for both skewness and kurtosis. Only the Raven's test and Trail Making Test part A & B had significant skewness and these variables were log-transformed before standardisation. The same adjustment and standardisation procedure was applied to the patient sample, using the normative standards from the control sample.

### **3.2.7 Data analysis**

Differences in socio-demographic and intellectual characteristics among the five groups were assessed using Analysis of Variance (ANOVA) models, Pearson Chi-Square or Fisher's Exact Test when appropriate. Differences in performance on each normative-adjusted neuropsychological measure between the five groups were examined using Analysis of Variance (ANOVA) models. The significance level was adjusted for multiple testing by Bonferroni correction, and was conservatively set at  $p \leq 0.003$  ( $0.05/16$ ). For descriptive purposes also the

following *a-priori defined* comparisons were carried out: First, each diagnostic group's performance was compared to the control group. Next, the following direct comparisons of performance between patients groups were conducted: Schizophrenia vs. Bipolar/manic; Schizophrenia vs. Depressive psychosis, and Bipolar/manic vs. Depressive psychosis. Significance level for these comparisons was set at  $p \leq 0.007$  ( $0.05/7$ ). Due to missing data on individual tests degrees of freedom varied slightly. Pearson's correlations were performed between each of the neuropsychological variables and three specific symptom dimensions: negative symptoms, reality distortion, and depression. ANOVA models were followed by analysis of covariance models (ANCOVA) which adjusted for IQ.



### 3.3 Results

#### 3.3.1 Demographic characteristics

**Table 3.1** presents demographic characteristics of the cohort. There were significant group differences in age ( $F=15.6$ ,  $df=4$ ,  $p<0.001$ ). Post hoc analysis revealed patients with schizophrenia, bipolar/manic and other psychotic disorders to be significantly younger than controls. The groups also differed significantly in gender distribution, with an excess of males in the schizophrenia group ( $\chi^2=12.73$ ,  $df=4$ ,  $p<0.013$ ). All groups significantly differed in measures of education ( $\chi^2=19.57$ ,  $df=8$ ,  $p<0.012$ ) but not in ethnicity ( $\chi^2=3.44$ ,  $df=4$ ,  $p=0.486$ ).

#### 3.3.2 Current and estimated premorbid IQ

There were overall significant group differences in current and estimated premorbid IQ (**Table 3.2**). Descriptive analyses demonstrated that compared to controls the schizophrenia and the other psychotic disorders groups had significantly lower scores on current and estimated premorbid IQ. The depressive psychosis group had a significantly lower current IQ score. The schizophrenia group also had significantly lower IQ scores compared to the bipolar/manic group. All of the above group differences reached the Bonferroni corrected level of significance ( $p\leq0.007$ ).

**Table 3.1 Demographic characteristics of diagnostic groups and healthy controls**

	Schizophrenia (N=65)		Other psychoses (N=46)		Depressive psychosis (N=39)		Bipolar/Manic (N=37)		Controls (N=176)		p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
<b>Age</b>	26.54	8.39	29.04	9.61	36.97	12.86	28.08	8.09	37.24	12.87	0.001
	N	%	N	%	N	%	N	%	N	%	
<b>Gender (Male)</b>	42	64.6	28	60.9	16	41.0	15	40.5	77	43.8	0.013
<b>Ethnicity (White)</b>	34	52.3	29	63.0	25	64.1	21	56.8	113	64.4	0.486
<b>Years of Education</b>											0.012
11 (compulsory)	44	67.2	35	76.0	27	68.4	17	45.9	84	47.7	
12-13 (post-compulsory)	15	23.0	8	17.4	6	15.8	11	29.7	52	29.5	
14 or more (college, graduate or post-graduate)	6	9.8	3	6.6	6	15.8	9	24.3	40	22.8	

**Table 3.2 IQ scores in diagnostic groups and healthy controls.**

	Schizophrenia (N=65) A		Other psychoses (N=46) B		Depressive Psychosis (N=39) C		Bipolar/Manic (N=37) D		Control (N=177) E		Overall I F value	P- value	Planned contrasts: Diagnostic groups vs. Controls*
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
<b>WAIS-R full scale IQ</b>	86.23	14.65	90.44	16.85	94.05	18.12	98.89	16.73	102.93	15.15	16.76	<0.000 1	A,B,C,<E A<D
<b>Estimated Premorbid IQ (NART)</b>	95.58	14.39	96.73	13.14	100.63	13.40	104.49	12.02	106.3	12.63	11.22	<0.000 1	A,B<E A<D

\* - Differences reached the Bonferroni corrected level of significance ( $p \leq 0.007$ )

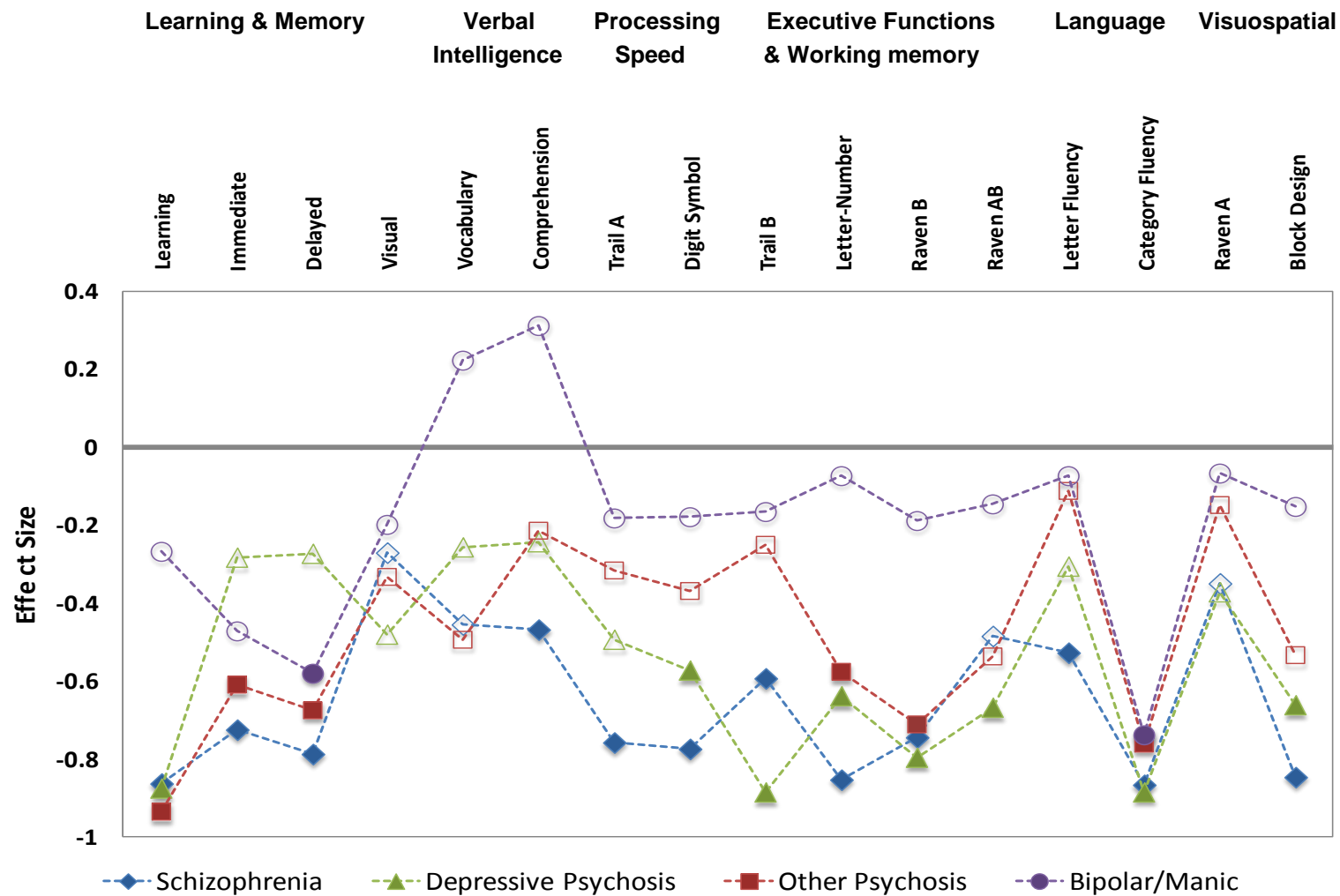
### 3.3.3 Neuropsychological performance

#### 3.3.3.1 Comparison between diagnostic groups and controls

ANOVA models demonstrated that for 10 of the 16 measures overall group differences reached the Bonferroni corrected level of significance ( $p \leq 0.003$ ). The measures that did not reach the Bonferroni corrected level of significance were Raven's set AB ( $p = 0.0033$ ), vocabulary ( $p = 0.009$ ), comprehension ( $p = 0.009$ ), and visual memory ( $p = 0.044$ ). No overall group differences were observed for the for Raven's A, and letter fluency ( $p\text{-values} > 0.05$ ).

The neuropsychological performance profiles of the four diagnostic groups and results of the descriptive analyses that followed the ANOVA models and compared each diagnostic group to controls are presented in **Figure 3.2**. The schizophrenia group presented a widespread impairment, and performed worse than controls on all measures (all  $p\text{-values} < 0.05$ ). For 12 of the 16 measures the differences also reached the Bonferroni corrected level of significance ( $p \leq 0.007$ ) (see **Figure 3.2**). The depressive psychosis and other psychotic disorders groups also demonstrated widespread impairments. Differences reached the Bonferroni corrected level of significance ( $p \leq 0.007$ ) for 8 and 6 measures respectively (**Figure 3.2**). In contrast, the bipolar/manic group performed significantly worse ( $p\text{-values} \leq 0.007$ ) than controls only on measures of delayed verbal memory, and Category fluency (**Figure 3.2**).

Figure 3.2 Neuropsychological performance among patients with various first-episode psychosis presentations



<sup>a</sup>Filled symbols represent a statistically significant difference between the diagnostic group and healthy comparison group at a Bonferroni-corrected level ( $p \leq 0.007$ ). Mean scores (comparison subjects set to zero) were calculated using all available diagnostic subjects per test (expressed in standardized [z] scores). Trail A=Trail Making Test, Part A; Trail B=Trail Making Test, Part B; Raven B=Raven's Coloured Progressive Matrices set B; Raven AB=Raven's Coloured Progressive Matrices set AB; Raven A=Raven's Coloured Progressive Matrices set A.

Pearson's correlation coefficients were also examined across patients groups between neuropsychological test scores and symptom dimensions. More severe negative symptoms were associated with poorer performance on Vocabulary ( $r=-0.193$ ,  $p=0.041$ ), Comprehension ( $r=-0.193$ ,  $p=0.043$ ), Digit Symbol ( $r=-0.38$ ,  $p=0.001$ ), Raven's B ( $r=-0.231$ ,  $p=0.018$ ), Trail Making Test part A ( $r=-0.270$ ,  $p=0.005$ ), Trail Making Test part B ( $r=-0.207$ ,  $p=0.036$ ), Rey Total Learning ( $r=-0.238$ ,  $p=0.014$ ), Letter fluency ( $r=-0.284$ ,  $p=0.006$ ), and Category fluency ( $r=-0.242$ ,  $p=0.02$ ). More severe reality distortion was associated with poorer performance only on Trail Making Test part B ( $r=0.252$ ,  $p=0.033$ ). Severity of depressive symptoms was not significantly associated with performance on any neuropsychological test.

### **3.3.3.2 Comparisons between diagnostic groups**

The bipolar/manic group performed better than the other patient groups on almost all neuropsychological measures. This group exhibited better performance compared to the schizophrenia group on measures of Vocabulary and Comprehension, Digit Symbol, Letter-Number Span, and Block Design, and these were statistically significant at the Bonferroni corrected level ( $p\text{-value} \leq 0.007$ ).

### **3.3.3.3 Role of general intellectual ability**

Differences in neuropsychological tests performance could be a function of current general intellectual ability (IQ). Therefore, in an exploratory analysis, I compared patient groups and controls while adjusting for current IQ. After adjustment, many of the specific neuropsychological differences were attenuated. None of the ANCOVA models reached a Bonferroni corrected level of significance, but a number of measures reached a conventional threshold of significance ( $p < 0.05$ ). These included the verbal learning ( $p=0.006$ ), category fluency ( $p=0.004$ ), and Letter-Number Span ( $p=0.017$ ) tests.

Descriptive analyses demonstrated that after adjustment for IQ the following comparisons were statistically significant at the Bonferroni corrected level of significance ( $p\text{-value} \leq 0.007$ ). The

schizophrenia group was significantly impaired compared to controls on the Letter-Number Span ( $p=0.003$ ) test. The depressive psychosis group was significantly impaired compared to controls on the verbal learning ( $p=0.003$ ), category fluency ( $p=0.004$ ) and Trail Making Test part B ( $p=0.006$ ) tests. The other psychoses group was significantly impaired compared to controls on the verbal learning ( $p=0.003$ ) test. The bipolar/manic group was significantly impaired compared to controls on the category fluency ( $p=0.003$ ) test. Direct comparisons between the diagnostic groups were not statistically significant at the Bonferroni corrected level.

### 3.4 Discussion

The aim of the first investigation was to compare neuropsychological performance between schizophrenia, bipolar/manic disorder, depressive psychotic disorder, other-psychotic patients and healthy controls. Despite extensive neuropsychological investigation in psychiatric disorders, this is the first epidemiological case-control investigation which includes a broad spectrum of psychotic patients with their first episode. The main findings of this investigation are that moderate to severe neuropsychological impairments characterize all psychotic disorders following the first psychotic episode, and that by-and-large, the magnitude of impairment on specific neuropsychological functions reflects a generalized cognitive deficit. Differences in neuropsychological performance between patient groups and controls, and between the different patient groups, were largely accounted for by differences in general intellectual ability.

This investigation is novel in several ways. First, this is the first study to examine neuropsychological function in the category of other psychotic disorders, a large clinical group, which have been difficult to study. Second, this is an ethnically diverse sample. Third, the availability of a well characterised, large, epidemiologically ascertained control group (which is difficult to obtain), which increases the validity and generalisability of findings. Fourth, the diagnostic procedures were blind to neuropsychological assessment.

Researchers have long debated the nature of the cognitive impairment in schizophrenia, particularly the relationship between cognition and psychosis, and whether schizophrenia is characterized by a generalized impairment versus independent deficits in specific cognitive impairments (Gold, 2004). Many neuropsychological investigations have sought to identify specific cognitive deficits that might represent more fundamental, so-called core impairments, reflecting underlying brain regions or networks related to the aetiology of the disorder (Jeste *et al.*, 1996, Reichenberg and Harvey, 2007, Seidman *et al.*, 2002). Similar investigations have been carried out with respect to other psychotic disorders. Determining if cognitive impairments are either more generalized across domains or more specific to particular domains also has important implications for clinical assessment, intervention design and genetic research (Gold, 2004). The results of this investigation highlight the degree of general cognitive impairment across psychotic disorders.



Studies of schizophrenia patients without a long history of illness or medication have documented a generalized deficit (Bilder *et al.*, 2000, Gold, 2004, Mohamed *et al.*, 1999), and these findings have been extended to chronic patients in a series of recent studies by Gold (Gold, 2004, 2008) that demonstrated that the cognitive deficit in schizophrenia is largely generalized across domains. Studies of generalized and specific neuropsychological functions in bipolar disorder and psychotic depression have been conducted in chronic patients (Quraishi and Frangou, 2002, Seidman *et al.*, 2002) and also suggest a generalized cognitive impairment.

Despite the evidence in this investigation that the cognitive deficit in psychotic disorders is generalized across cognitive domains, additional, specific deficits were apparent. In schizophrenia, a selective deficit in working memory was evident. Working memory involves the ability to maintain and manipulate information over short periods of time, and has been associated with frontal-lobe function (Callicott *et al.*, 2003, Reichenberg and Harvey, 2007). Deficits in working memory have been implicated as potential core deficits in schizophrenia (Elvevag and Goldberg, 2000), and working memory processes have been shown to share a genetic basis with schizophrenia (Toulopoulou *et al.*, 2007).

A deficit, beyond general intellectual impairment in verbal learning was evident in the psychotic depression and other psychoses groups. A selective impairment in memory and learning in schizophrenia has been previously hypothesized (Saykin *et al.*, 1991), and has been associated with the temporal-hippocampal region (Reichenberg and Harvey, 2007). The lack of diagnostic specificity observed in this investigation merits further examination.

The Category (semantic) fluency test was selectively impaired, beyond general intellectual impairment, in the psychotic depression, and bipolar/manic groups. This test involves the capacity to generate words belonging to a particular category and has been associated with frontal and temporoparietal function (Lezak, 1995). The letter (phonemic) fluency test was not selectively impaired. The disproportionate semantic fluency impairment may be due to abnormal semantic organization (Kremen *et al.*, 2003).

Family, twin and molecular genetic studies suggest that schizophrenia and affective psychotic disorders may share certain susceptibility genes, and there is a clear overlap in phenomenological symptoms (Craddock *et al.*, 2005, 2007, Murray *et al.*, 2004). However, from a developmental perspective there are some differences. There is a large and consistent literature documenting childhood cognitive impairments preceding schizophrenia (Cannon *et al.*, 2002b, Jones *et al.*, 1994, Reichenberg *et al.*, 2002). Broadly defined affective psychosis has also been shown to be preceded by developmental impairment, but the effects are not as strong (van Os *et al.*, 1997, Zammit *et al.*, 2004), and seem to be confined to early-onset cases (van Os *et al.*, 1997). Premorbid intellectual functioning was relatively intact in bipolar/manic patients in the present study as it was in the Dunedin cohort study (Cannon *et al.*, 2002b). This may suggest that the onset of psychosis is associated with the appearance of a generalized deficit, superimposed upon a varying level of premorbid intellectual reserve, least in schizophrenia and greatest in bipolar disorder.

This investigation has a number of strengths. It is a large first episode psychosis study incorporating a population-based epidemiological sample. The fact that a large normal comparison group was included also strengthens interpretation of the results. Limitations of this investigation should, however, be acknowledged. One limitation is that no patients were drug naïve. Unfortunately I had insufficient information on medication to reliably determine dosage. Medication type or side effects could influence subjects' neuropsychological performance. Nevertheless, only weak correlations between neuropsychological functioning and symptom severity were observed. Another limitation is that patients were assessed soon after their first admission. Diagnostic changes may occur over time. However, Schwartz *et al.* (Schwartz *et al.*, 2000) followed up a large sample of first admission psychotic patients, and diagnostic consistency at 24 months after first admission was high for schizophrenia (92%), bipolar disorder (83%) and psychotic depression (74%). The most frequent shift in diagnosis at 24 months was to schizophrenia-spectrum disorders.

In summary, these results add to the evidence indicating that early in their course, cognitive deficits are present in all psychotic disorders but are most severe and pervasive in schizophrenia

and least so in bipolar/manic disorder. They also add to the growing body of clinical, neurophysiological and genetic evidence supporting a continuum between schizophrenia and psychotic affective disorders (Murray *et al.*, 2004).

## **Chapter 4 Gender differences in the profile of neuropsychological performance in patients with first episode of psychosis**

### **4.1 Introduction**

It is well established that patients with schizophrenia and other psychosis exhibit a wide range of neuropsychological deficits (Reichenberg *et al.*, 2009, Zanelli *et al.*, 2010). An unresolved question, however, is whether there are gender differences in cognitive performance. The existing literature suggests that there are pronounced sex differences in schizophrenia, including differences in age of onset, clinical symptoms, brain structure and outcome (Narr *et al.*, 2001, Shipman *et al.*, 2009). For example, on average, males have earlier age of onset, longer and more frequent acute psychotic episodes, while females show better premorbid function, less negative symptoms, better response to antipsychotic medication and more positive symptoms (Rubin *et al.*, 2008, Shipman *et al.*, 2009).

In terms of neuropsychological function, evidence concerning schizophrenia is mixed. While some studies report less severe cognitive impairments in female patients on most cognitive domains (Dickinson *et al.*, 2010, Goldstein *et al.*, 1998, Leung and Chue, 2000) other studies found that females exhibited greater cognitive deficits (Lewine *et al.*, 1996, Perlick *et al.*, 1992). Some research failed to find any significant gender differences in cognition in schizophrenia (Andia *et al.*, 1995, Goldberg *et al.*, 1995, Gur *et al.*, 2000, Hoff *et al.*, 1998, Shipman *et al.*, 2009), and yet others reported domain-specific gender differences, with males showing greater impairments than females in sustained attention, language, executive function and intelligence (Goldstein *et al.*, 1998, Haas *et al.*, 1991, Kopala and Clark, 1990, Seidman *et al.*, 1997).

The question of gender differences in neuropsychological function in other psychotic disorders has rarely been examined. Carrus *et al.* (Carrus *et al.*, 2010) reported that in bipolar patients, males underperformed females on immediate memory tasks (encoding and retrieval processes). Barrett *et al.* (Barrett *et al.*, 2008) also noted that male patients underperformed female patients in measures of spatial working memory. These studies did not find gender differences in

performance on measures of planning, attentional set-shifting, verbal fluency, general intellectual ability, response inhibition and other executive functions.

However most of the studies that examines neuropsychological function in psychosis by gender examined patients with established illness and thus performance may have been impaired by issues concerning treatment or illness course. In this investigation I examined gender differences in neuropsychological function in first episode patients with a range of psychotic illnesses, including schizophrenia, bipolar/manic and depressive psychoses. Four features of this investigation are especially important. First, this investigation examines a large epidemiological cohort of first-episode psychosis patients with neuropsychological data. Second, a large community control sample was epidemiologically ascertained, giving detailed and reliable norms for comparison. Third, a comparison across diagnostic groups is a unique feature of this investigation. Finally, both patient and comparison samples are ethnically diverse, thus increasing the potential generalisability of results.

#### **4.1.1 Aims and objectives**

The main objective is to investigate whether there are gender differences in the profile of neuropsychological performance in patients with first episode of psychosis. Because of the conflicting results in previous research, which examined cognition particularly in schizophrenia, no a priori hypothesis regarding gender differences in neuropsychological performance was made. The thesis describes methodology and presents the findings of the investigation with the aim of developing a greater understanding of the gender differences particularly in affective disorders.

## 4.2 Materials and methods

### 4.2.1 The analytic cohort

The analytic cohort comprised of male and female patients who had a consensus ICD-10 diagnosis of schizophrenia or schizoaffective disorder (M=45, F=25), bipolar/mania (M=14, F=20), depressive psychosis (M=15, F=21) and 148 healthy controls (M=67, F=81). For all cases and controls there were complete interview data as well as: a) IQ measurements on the National Adult Reading Test (NART) (Nelson and Willison, 1991), and a short form of the Wechsler Adult Intelligence Scale – Revised (WAIS-R) (Wechsler, 1981); and b) a neuropsychological battery. Cases and controls were required to be native speakers of English or to have migrated to the UK by age 11. The latter requirement ensured that each participant had a good command of English as a non-native language as they would have completed at least their secondary education in the UK, thus minimising the effect of linguistic or cultural biases on the performance of a multi-ethnic sample. In accordance with previous studies (Reichenberg *et al.*, 2009), cases or controls with missing data on more than three neuropsychological measures were excluded.

### 4.2.2 Neuropsychological assessment

Sixteen neuropsychological measures were selected to assess six broad cognitive domains: (1) Learning and Memory (verbal and visual); (2) Executive functions and working memory; (3) Attention, concentration and mental speed; (4) Language; (5) Visual constructual/perceptual abilities, and (6) WAIS-R verbal intelligence.

1. **Learning and memory: verbal** ( *short-term verbal immediate recall and delayed verbal recall*) were assessed using trials 1–5, 6 and 7, respectively, of the Rey Auditory Verbal Learning Test (RAVLT) and **visual** ( *immediate and delayed recall*) was examined using Visual Reproduction of the Wechsler Memory Scale - Revised (WMS-R) (Wechsler, 1987).
2. **Executive functions and working memory** were evaluated using the Trail Making Test - part B, Letter-Number Span, and Sets AB and B of Raven's Coloured Progressive Matrices (CPM)

3. **Attention, concentration and mental speed** were measured using Trail Making - part A and the WAIS-R Digit Symbol subtest.
4. **Language** was evaluated using the Semantic Fluency (categories 'body parts', 'fruits' and 'animals'), and Letter Fluency (letters F, A, S).
5. **Visual-construction/perceptual abilities** were assessed using set A of Raven's Coloured Progressive Matrices and the WAIS-R Block Design.
6. **WAIS-R verbal intelligence** was assessed by the WAIS-R Vocabulary and Comprehension sub tests.

Premorbid intelligence was estimated using the National Adult Reading Test (NART) (Nelson and Willison, 1991). Full-scale IQ was derived from the WAIS-R (Wechsler, 1981) subtests in the neuropsychological testing battery.

(Full description; please see chapter 3.2.4 Neuropsychological assessment).

#### **4.2.3 Data analysis**

Gender differences in socio-demographic characteristics, symptom severity and measures of IQ among the three diagnostic groups were assessed using Analysis of Variance (ANOVA) models, Pearson Chi-Square or Fisher's Exact Test when appropriate. For descriptive purposes I carried the following *a-priori defined* comparisons: for each diagnostic group male and female patient performance on the normative-adjusted neuropsychological measures was compared to the performance of the control group using ANOVA models. Gender differences in performance on the normative-adjusted neuropsychological measure among the three diagnostic groups were examined using a Repeated Measures Analysis of Variance (ANOVA) model. Domain scores were computed as the average of scores of the tests comprising each of the six domains described in the previous section. These domain scores were used in the analysis. Due to missing data on individual tests, degrees of freedom varied slightly. ANOVA was used to examine gender difference on symptom dimensions: negative symptoms, reality distortion, depressive symptoms, disorganization and manic symptoms.

#### **4.2.4 Creating gender-specific norms for neuropsychological tests**

A regression based approach was used to create gender-specific normative standards for the neuropsychological tests. This was done separately for males and females. Age, ethnicity and education were regressed on each of the neuropsychological measures in the healthy sample of males and females. Then, scores were adjusted on the basis of these regression results and standard (i.e., Z) scores were created. The regression corrected scores were also inspected for both skewness and kurtosis. Only the Raven's test and Trail Making Test part A & B had significant skewness and these variables were log-transformed before standardisation. The same adjustment and standardisation procedure was applied to the male and female patient sample, using the normative standards from the control sample.



## 4.3 Results

### 4.3.1 Demographic characteristics

**Table 4.1** presents the demographic characteristics of male and female patients in the three diagnostic groups and healthy controls. The groups differed significantly in gender distribution ( $\chi^2=9.98$ ,  $df=3$ ,  $p=0.03$ ), with a higher proportion of males in the schizophrenia group compared with the bipolar/manic and depressive psychosis groups. Gender differences in ethnic origin were only evident in the bipolar/manic group ( $\chi^2=5.55$ ,  $df=2$ ,  $p<0.018$ ), with higher proportion of non-white females. Age of onset was higher for females compared with males in the schizophrenia group ( $t=-2.58$ ,  $p=0.012$ ). There were no significant gender differences in level of education.

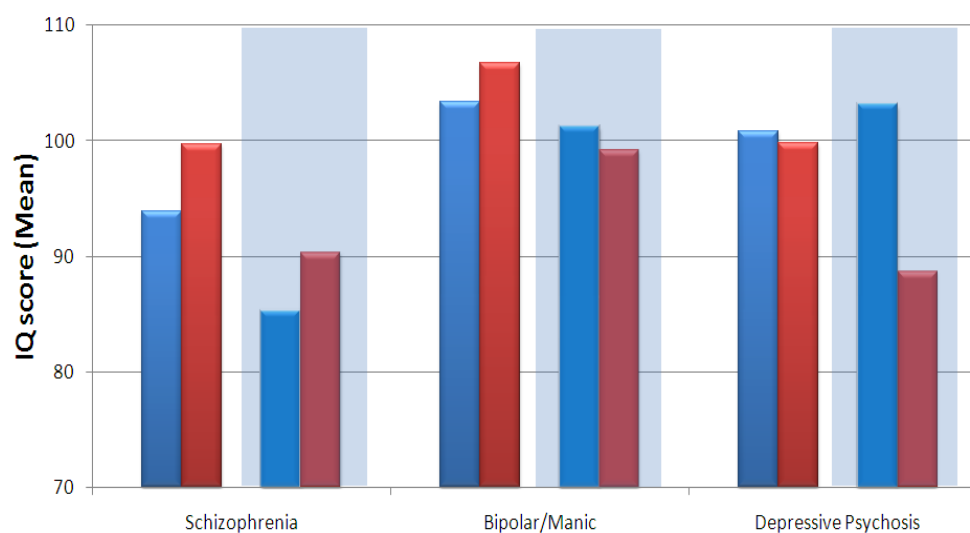
**Table 4.1 Demographic characteristics of males and females patients with first-episode of psychosis and healthy controls**

	<b>Schizophrenia</b>		<b>Bipolar/Manic</b>		<b>Depressive Psychosis</b>		<b>Controls</b>	
	<i>Males</i> (N=45)	<i>Females</i> (N=25)	<i>Males</i> (N=14)	<i>Females</i> (N=20)	<i>Males</i> (N=15)	<i>Females</i> (N=21)	<i>Males</i> (N=67)	<i>Females</i> (N=81)
<b>Age (<math>\pm</math>SD)</b>	24.9 $\pm$ 6.5	30.4 $\pm$ 11.4	26.0 $\pm$ 5.8	30.9 $\pm$ 8.7	33.2 $\pm$ 12.6	40.5 $\pm$ 12.7	39.2 $\pm$ 13.2	38.8 $\pm$ 12.4
<b>Years of Education</b>								
11 ( <i>compulsory</i> )	64.4%	60.0%	35.7%	50.0%	53.3%	76.2%	38.8%	55.6%
12-13 ( <i>post-compulsory</i> )	28.9%	20.0%	50.0%	15.0%	20.0%	14.3%	32.8%	27.2%
14 ( <i>college, graduate, post-graduate</i> )	6.7%	20.0%	14.3%	35.0%	26.7%	9.5%	28.4%	17.2%
<b>Ethnicity Caucasian</b>	60.0%	60.0%	85.7%	45.0%	60.0%	66.7%	70.1%	81.5%

### 4.3.2 Current and estimated premorbid IQ

Male and female current and estimated premorbid IQ in the three diagnostic groups are shown in **Figure 4.1** Males and females were compared to controls on current and estimated premorbid IQ measures using ANOVA models. The significance level was adjusted for multiple testing by Bonferroni correction and was conservatively set at  $p \leq 0.0125$  ( $0.05/4$ ).

**Figure 4.1** Estimated premorbid and current (shaded areas) IQ in males (blue bars) and females (red bars) across diagnostic groups: schizophrenia (N=45 males, N=25 females); bipolar/manic (N=14 males, N=20 females), and depressive psychosis (N=15 males, N=21 females)



#### **4.3.2.1 Comparison to controls**

In the schizophrenia group, females performed significantly worse than healthy controls only on current IQ, whereas males performed significantly worse on both current and estimated premorbid IQ. In the bipolar/manic group there were no significant gender differences. In the depressive psychosis group, females performed significantly worse on current IQ compared with controls.

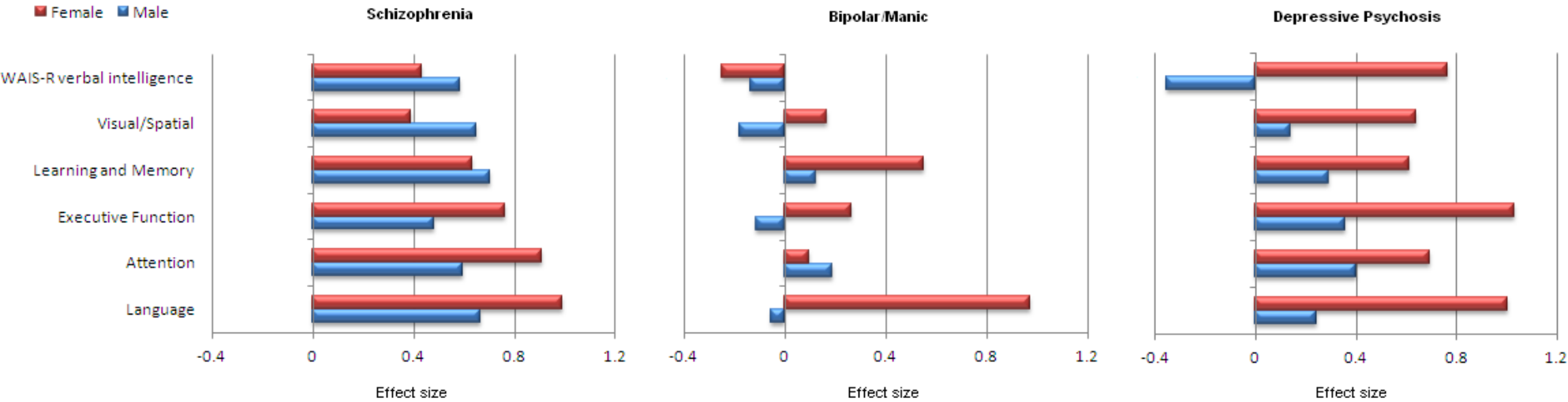
#### **4.3.2.2 Comparison of males and females within diagnostic groups**

Analysis of variance (ANOVA) revealed a significant effect of diagnosis on current IQ ( $F=7.298$ ,  $df=2$ ,  $134$ ,  $p=0.001$ ), but no significant effect of gender ( $F=1.674$ ,  $df=1$ ,  $134$ ,  $p=0.198$ ). However, there was a significant gender by diagnosis interaction effect ( $F=4.216$ ,  $df=5$ ,  $134$ ,  $p=0.017$ ), where females in the depressive psychosis group exhibited lower scores than males. There was a significant effect of diagnosis on premorbid IQ ( $F=3.912$ ,  $df=2$ ,  $129$ ,  $p=0.022$ ) but no significant effect of gender ( $F=1.171$ ,  $df=1$ ,  $129$ ,  $p=0.281$ ), or gender by diagnosis interaction ( $F=0.674$ ,  $df=5$ ,  $134$ ,  $p=0.511$ ).

### **4.3.3 Neuropsychological performance**

**Figure 4.2** presents neuropsychological test performance in males and females for each of the three diagnostic groups.

Figure 4.2 Effect size of impairment in neuropsychological functioning in males (blue bars) and females (red bars) according to diagnostic groups: schizophrenia (N=45 males, N=25 females); bipolar/manic (N=14 males, N=20 females), and depressive psychosis (N=15 males, N=21 females) *Note: Impairments are represented by positive values on scale.*



#### 4.3.3.1 Comparison to controls

Males and females were compared to controls on each neuropsychological domain using ANOVA models. The significance level was adjusted for multiple testing by Bonferroni correction and was conservatively set at  $p \leq 0.008$  ( $0.05/6$ ). In the schizophrenia group, females performed significantly worse than healthy controls on learning, attention, executive function and language domains whereas males performed significantly worse on all domains. In the bipolar/manic group, females performed significantly worse than healthy controls on neuropsychological domains assessing language and learning, whereas males performance was similar to that of controls. In the depressive psychosis group females performed significantly worse than controls on all neuropsychological domains. There were no significant differences between males and healthy controls.

#### 4.3.3.2 Comparison of males and females within diagnostic groups

A repeated-measures ANOVA of gender, diagnosis and neuropsychological domain showed a significant effect of gender ( $F=5.08$ ,  $df=1$ ,  $112$ ,  $p=0.026$ ) and of diagnostic group ( $F=4.342$ ,  $df=2$ ,  $112$ ,  $p=0.001$ ), but no significant gender by diagnosis interaction ( $F=1.458$ ,  $df=2$ ,  $112$ ,  $p=0.237$ ). However, there was a significant three-way interaction between gender, diagnosis and neuropsychological domain ( $F=2.123$ ,  $df=10$ ,  $112$ ,  $p=0.021$ ), indicating that the profile of neuropsychological impairment varies as a function of both diagnosis and sex. To further examine the three way interaction in detail, separate analyses for each diagnostic group were repeated. In the schizophrenia group there was no significant effect of gender ( $F=0.079$ ,  $df=1$ ,  $55$ ,  $p=0.78$ ) and no significant gender by neuropsychological domain interaction ( $F=1.904$ ,  $df=5$ ,  $55$ ,  $p=0.094$ ) (**Figure 4.2**). Differences between males and females in neuropsychological performance were small - not greater than 0.3 standard deviation ( $ES < 0.3$ ). Females performed worse than males on language, attention and executive function domains and better than males on WAIS-R verbal intelligence and visual-spatial domains. In the bipolar/manic group there was no significant gender effect ( $F=1.604$ ,  $df=1$ ,  $25$ ,  $p=0.217$ ) but there was a significant gender by neuropsychological domain interaction ( $F=2.854$ ,  $df=5$ ,  $p=0.018$ ). Females performed worse than males on language, executive function, learning and memory, and visual/spatial domains with effect size of difference ranging between 0.2 to 1. Post hoc contrasts revealed a significant difference on the language

domain ( $t=2.37$ ,  $df=25$ ,  $p=0.026$ ), with females performing worse than males ( $ES=-1.05$ ). In the depressive psychosis group there was a significant effect of gender ( $F=5.729$ ,  $df=1$ ,  $p=0.023$ ) but no significant gender by neuropsychological domain interaction ( $F=1.229$ ,  $df=5, 32$ ,  $p=0.298$ ). Females performed worse than males on all neuropsychological domains (**Figure 4.2**) with effect sizes of difference ranging from 0.6 to 0.4.

#### **4.3.3.3 Symptom severity and neuropsychological performance**

I examined gender differences in symptom severity in these diagnostic groups (**Table 4.2**). There were no significant gender differences in symptom severity in any diagnostic group, with the exception of disorganisation symptoms in schizophrenia where males had more severe symptoms than females ( $p=0.038$ ). I also examined the associations between symptoms severity and neuropsychological performance in males and females in each diagnostic group. No consistent pattern of association emerged. The overwhelming majority of correlation coefficients were small and not statistically significant (data available on request)

**Table 4.2 Descriptive Statistics for Test of Gender Differences between Neuropsychological Scores and Symptom Dimensions**

	<b>Schizophrenia</b>		<b>Bipolar/Manic</b>		<b>Depressive Psychosis</b>	
	<i>Males</i> (N=45)	<i>Females</i> (N=25)	<i>Males</i> (N=14)	<i>Females</i> (N=20)	<i>Males</i> (N=15)	<i>Females</i> (N=21)
<b>Symptom Dimensions</b>						
<i>Manic Symptoms</i>	1.6±2.6	1.7±2.8	6.2±3.3	5.6±3.3	3.3±4.1	0.3±0.5
<i>Depressive Symptoms</i>	1.4±1.7	1.6 ±2.0	1.1±1.6	0.8±1.6	3.1±1.6	3.5±1.5
<i>Reality Distortion</i>	4.1±2.3	3.8±2.1	2.2±2.6	3.8±1.0	3.0±2.0	3.6±1.7
<i>Negative Symptoms</i>	2.2±2.2	1.7±2.8	0.4±0.5	1.1±1.8	2.1±1.7	1.9±2.0
<i>Disorganization</i>	1.3±0.9	0.6±0.7	0.7±1.5	0.3±0.5	0.1±0.3	0.5±0.9



## 4.4 Discussion

To the best of my knowledge, this is the first population-based epidemiological study of gender differences in neuropsychological performance across a range of psychotic disorders. It provides new evidence to what is known about the cognitive impairment in psychoses in two important ways. First, while both males and females with schizophrenia showed pervasive neuropsychological impairments, males with bipolar/manic or psychotic depressive disorders showed no significant impairments compared with healthy controls. Second, the investigation shows that gender differences in neuropsychological functions are disorder specific. Gender differences were evident in psychotic depression but not in schizophrenia. There was also evidence of a gender based domain- specific impairment in bipolar/manic disorder. Females performed significantly worse than males on the language domain. Gender differences were not due to differences in symptom severity.

Both males and females with schizophrenia showed generalized and clinically severe cognitive impairments. There were no statistically significant gender differences in neuropsychological performance in schizophrenia. Previous studies reported mixed results (Goldstein *et al.*, 1998, Hoff *et al.*, 1998, Seidman *et al.*, 1997). Hoff *et al.* (Hoff *et al.*, 1998) studying first episode and chronic schizophrenia patients reported that after controlling for symptom severity there were no sex differences in cognition between male and female patients with schizophrenia. Other studies reported domain-specific gender differences with males showing greater impairments than females in sustained attention, language, executive function and intelligence (Goldstein *et al.*, 1998, Haas *et al.*, 1991, Kopala and Clark, 1990, Seidman *et al.*, 1997). The results of this investigation indicate that the well replicated finding of a severe cognitive impairment in schizophrenia is equivalent in males and females at least at onset (Dickinson *et al.*, 2004, Knowles *et al.*, 2010, Reichenberg and Harvey, 2007).

In the bipolar/manic group, males showed no cognitive impairments. Gender differences were evident in the language domain, where females performed statistically significantly worse than males. The impairment in the language domain was very large (more than 1SD compared to controls). Whereas, Barret *et al.*, (Barrett *et al.*, 2008) and Carrus *et al.* (Carrus *et al.*, 2010) found

that males underperformed females on immediate memory and spatial working memory tasks, I saw no evidence for gender differences on related neuropsychological domains. The studies by Barret et al., (2008) and Carrus et al., (2010) however, used clinical, not epidemiological samples and studied older, and more severe patient samples.

I am not familiar with other studies examining gender differences in neuropsychological functioning in patients suffering from depressive psychosis. My data showed distinct cognitive patterns in this patient population. Females were impaired across all neuropsychological domains compared to males. Males showed relatively preserved cognitive ability.

One possible explanation for my finding could be female-specific vulnerability to the effects of psychotic illness and medication. Antipsychotic medications have been shown to adversely effect cognition (Arnsten *et al.*, 1994). However, severity of neuropsychological impairments in females was not identical across domain and disorders. Therefore a complex interaction of medication and vulnerability would be required in order to support this explanation. Alternatively, the tentative nature of diagnosis on first presentation may help explain some of the findings. Patients were assessed 6 months after their first admission. Previous research has shown that while a schizophrenia diagnosis is reasonably stable, 20% of bipolar and 30% of major depression will shift diagnosis to schizophrenia spectrum within 24 months of their first admission (Longenecker *et al.*, 2010, Schwartz *et al.*, 2000). One could speculate that if such a diagnostic shift was more likely to be found in female patients it could help explain the findings.

This investigation has several strengths. It is a large, first-episode psychosis study incorporating a population-based epidemiological sample. A limitation of most previous studies is that they used clinical rather than epidemiological samples. Clinical samples involve patient series, not complete populations. As a result, it is difficult to generalize from studies using clinical samples. The fact that a large healthy comparison group was included also strengthens the interpretation of my results. However, the following limitation of this investigation should also be acknowledged. I had insufficient information on medication to reliably determine dosage, and no patients were drug

naive. Medication type and side effects can influence subjects' neuropsychological performance. Nevertheless, I observed only weak correlations between neuropsychological functioning and symptom severity.

In summary, the results of this investigation indicate that early in the course of psychotic illness, gender related factors appear to moderate the severity of cognitive deficits in bipolar/mania and depressive psychosis patients. In contrast, gender related factors have only minimal effects on the neuropsychological impairment in schizophrenia. Such knowledge may be valuable in designing cognitive-targeted intervention in psychosis.

## **Chapter 5 The course of neuropsychological impairment over the first decade of illness**

### **5.1 Introduction**

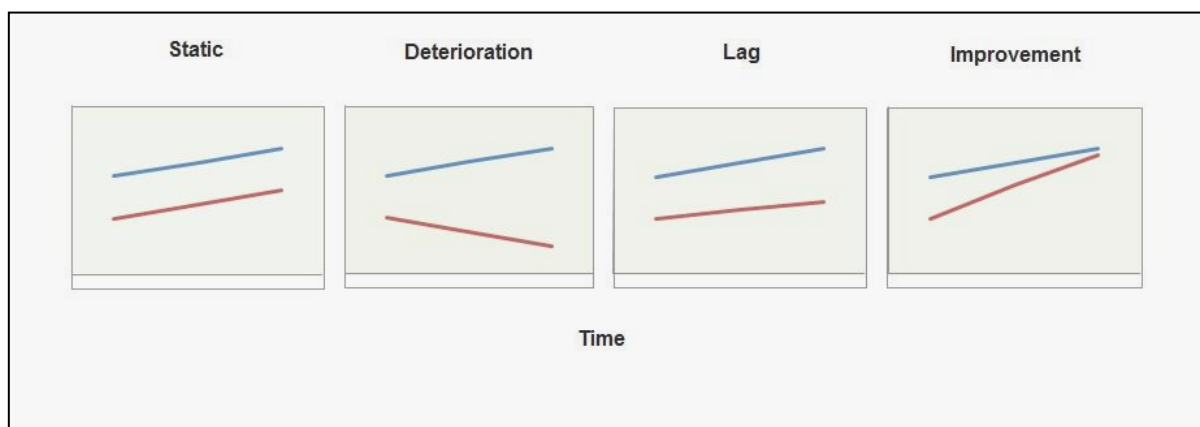
The longitudinal course of the cognitive dysfunction in psychoses has yet to be fully clarified. Whereas some studies in chronic institutionalized patients have revealed a progressive decline in cognitive abilities, studies of first episode patients have indicated that initial cognitive deficits might remain stable over time. Applying a longitudinal design studies have explored the trajectory of cognitive dysfunction in first episode psychosis. However, follow-up studies are complex to carry out, expensive, very demanding and time consuming for both researchers and participants. Neuropsychological tests, in particular, can be difficult to complete by psychotic patients purely due to lack of motivation or failure to understand tasks, or not remembering the instructions (Barnett *et al.*, 2010). Also, issue of attrition can have a negative effect on prospective longitudinal studies of cognition (Keefe and Harvey, 2008, Kurtz *et al.*, 2005). In other words, attrition occurs in instances where participants drop out of the study or it is impossible to trace them. As a result, a number of participants diminish in the follow up part which consequently affects the generalisability and possible bias of the findings (Menard, 2002).

#### **5.1.1 Longitudinal studies of neuropsychological profile in first episode psychosis: review of the literature**

The natural course of cognitive dysfunction remains under debate. Whether cognitive dysfunction is stable, declines or even improves over time or whether there is time-related variability in deficit profiles is still unclear. Four hypotheses put forward to describe the course of the cognitive impairment in schizophrenia are illustrated in **Figure 5.1**. The static deficit hypothesis (Hoff *et al.*, 1999, Leeson *et al.*, 2009a, Leeson *et al.*, 2009b, Nopoulos *et al.*, 1994, Rund, 1998, Rund *et al.*, 2007, Sweeney *et al.*, 1991) predicts static cognitive impairment, manifested as deficits that are evident during or soon after the first episode and remain stable. The deterioration hypothesis (Oie *et al.*, 2008) predicts decline in cognitive performance following the first episode. The amelioration hypothesis suggests improvement over time in cognitive performance (Addington *et al.*, 2005, Gold *et al.*, 1999, Hoff *et al.*, 1991, Rodriguez-Sanchez *et al.*, 2008, Scottish Schizophrenia

Research Group, 1988). Finally, the lag hypothesis (Hoff *et al.*, 1999) predicts growth in cognitive abilities, but growth that lags behind the more rapid growth in healthy individuals.

**Figure 5.1** Schematic representation of four hypotheses of the course of cognitive functioning in schizophrenia (The blue line represents healthy comparison subjects and the red line represents individuals with schizophrenia).



The very first longitudinal study was reported by Moran *et al.*, in 1960 (Moran *et al.*, 1960). The authors studied a sample of 55 not medicated paranoid schizophrenic patients using a word meaning measure and then followed them up 6 years later (N=30). Moran *et al.*, (1960) (Moran *et al.*, 1960) reported remarkable stability over time but a slight decline found in performance on definitions. This was explained by normal aging process rather than with increased schizophrenic pathology or length of hospitalization. A methodological strength in this study was that the patients were probably not medicated (Moran *et al.*, 1952). In more recent years, there have been an increasing number of longitudinal studies of first episode psychosis. Summary of the neuropsychological results of all such known studies in chronological order of publication date is presented in **Table 5.1**. Like the review of Rund (Rund, 1998), Hoff *et al.*, (Hoff *et al.*, 2005) and Bozikas & Andreou (Bozikas and Andreou, 2011) studies indicate either an improvement in cognitive function or stability of functions in the first several years of illness.

Close inspection of **Table 5.1** indicates that the majority of longitudinal studies of the course of neuropsychological functioning had a follow-up time of only 1– 4/5 years (Addington *et al.*, 2005, Albus *et al.*, 2006, Albus *et al.*, 2002, Bilder *et al.*, 1991, Censits *et al.*, 1997, de Mello Ayres *et al.*, 2010, Hill *et al.*, 2004, Hoff *et al.*, 1991, Hoff *et al.*, 2005, Leeson *et al.*, 2009b, Mayoral *et al.*, 2008, Nopoulos *et al.*, 1994, Rodriguez-Sanchez *et al.*, 2008, Rund *et al.*, 2007, Scottish Schizophrenia Research Group, 1988, Sweeney *et al.*, 1991, Zipparo *et al.*, 2008). Only five studies had a follow-up time of more than 4/5 years of illness (Gold *et al.*, 1999, Hoff *et al.*, 1999, Leeson *et al.*, 2009a) with three studies reporting a follow-up of ten years or more (Hoff *et al.*, 2005, Oie *et al.*, 2008, Stirling *et al.*, 2003).

**Table 5.1 Review of longitudinal neuropsychological studies of first episode (FE) psychotic patients with a length of follow-up of one or more year.**

Study		Subjects	Follow-up (years)	Findings
Scottish Sz Research Group (1988)		49 FE schizophrenia	1	<b>Improvement</b> on Ravens Progressive Matrices, block design, and digit copy; unchanged in vocabulary and similarities
Hoff et al., (1991)		15 FE schizophrenia	2	<b>Improvement</b> on executive, concentration/speed, and global scales
Bilder et al., (1991)		28 FE schizophrenia	1	High <b>stability</b> in neuropsychological deficit. <b>Improvement</b> on most functional domains (attention, memory, motor functions). <b>Decline</b> on attentional span (digit span)
Sweeney et al., (1991)		15 FE schizophrenia 24 chronic patients	1	High <b>stability</b> on memory, verbal fluency, verbal learning/recall, visual memories <b>Improvement</b> on verbal recognition memory, orientation, psychomotor skills (Trails A and B, digit symbol, finger tapping-nondom, line orientation, verbal recognition memory on Rey auditory verbal learning test)
Nopoulos et al., (1994)		35 FE schizophrenia	1 - 2	High <b>stability</b> . <b>Improvement</b> on complex attention and executive function
Censits et al., (1997)		30 FE schizophrenia 30 previously treated	1.58 (19 months)	High <b>stability</b> (no decline) There were no differences in neuropsychological performance over time between first-episode and previously treated patients.
Hoff et al., (1999)		42 FE schizophrenia 16 normal controls	4 - 5	High <b>stability</b> . Patients did not improve as much as controls on verbal memory and sensory-perceptual functions
Gold et al., (1999)		21 FE schizophrenia 33 recent onset schizophrenia	5	<b>Improvement</b> on performance and Full Scale IQ, letter cancellation, logical memory-immediate, WCST categories, <b>decline</b> in dominant and non-dominant finger tapping

Table 5.1 (continued)			
Study	Subjects	Follow-up (years)	Findings
Albus et al., (2002)	50 FE schizophrenia 50 normal controls	2	<b>Stability</b> of cognitive domains in patients over time except of <b>improvement</b> on verbal memory scale and absence of improvement on visual memory; visual-motor processing/attention and abstraction/flexibility did not change
Stirling et al., (2003)	24 FE schizophrenia	10 -12	High <b>stability</b> on measures of executive/frontal function. <b>Decline</b> on object assembly, picture completion, and memory for designs.
Hill et al., (2004)	45 FE schizophrenia 33 normal controls	1 - 2	<b>Stability</b> in verbal memory and other functions through 2 year period
Hoff et al., (2005)	21 FE patients (13 schizophrenia; 6 schizoaffective; 2 recovered (asymptomatic)) 8 controls	10	<b>Improved</b> performance (patients and controls as a group) in verbal intellectual functioning, the Stroop Color–Word test, and motor speed. Patients actually <b>improved</b> more than controls on a measure of immediate visual memory. Relative <b>stability</b> through at least 10 years of illness.
Addington et al., (2005)	105 FE psychosis (all time point) 66 controls (1 year)	1 - 3	<b>Improvement</b> in patients over the 3 year period in several subsets. But in the 1 <sup>st</sup> and 2 <sup>nd</sup> year – patients failed to improve on verbal fluency, visual memory, visuomotor sequencing and the Stroop, whereas controls failed to improve on auditory verbal learning, WCST and psychomotor speed
Albus et al., (2006)	71 FE schizophrenia 71 controls	2 - 5	<b>Improvement</b> in both groups over time in the majority of subtests. Slight deterioration in verbal fluency in patients
Rund et al., (2007)	138 FE psychosis (at 1 year follow-up) 111 FE psychosis (at 2 year follow-up)	1 - 2	High <b>stability</b> or slight <b>improvement</b> on most of neurocognitive domains (with the most significant improvement during the first year).



Table 5.1 (continued)			
Study	Subjects	Follow-up (years)	Findings
Rodríguez-Sánchez et al., (2008)	112 FE schizophrenia 22 controls	1	<b>Improvement</b> in cognitive performance in virtually all the cognitive domains after one year. However, patients continued to show marked cognitive deficits after one year, unlike healthy volunteers. The longitudinal cognitive changes were similar in patients and controls in all domains except verbal memory
Øie et al., (2008)	15 FE schizophrenia	13	<b>Decline</b> in neuropsychological performance particularly in verbal memory, attention, and processing speed.
Mayoral et al., (2008)	24 FE psychosis 29 controls	2	<b>Improvement</b> in almost all cognitive domains. However, this improvement disappeared in the patient group after controlling for improvement in symptomatology
Zipparo et al., (2008)	32 FE schizophrenia	2 - 3	Overall <b>improvement</b> in cognitive functioning over the follow-up interval, they also exhibited a slight (non-significant) <b>decline</b> in verbal learning and memory over the same period
Leeson et al., (2009)	60 FE schizophrenia 27 controls	1 - 3	Patients with preserved IQ or deteriorated IQ at baseline showed similar IQ <b>improvement</b> as controls whereas patients with low IQ at baseline showed less improvement. Similar changes in memory and executive function in patients and controls
Leeson et al., (2009)	104 FE schizophrenia 25 controls 31 FE schizophrenia 25 controls	1 - 3 6	<b>Stability</b> in measures of learning from feedback over 3 and 6 years. However, patient self-shifting performance over the first year was inconsistent
de Mello Ayres et al., (2010)	56 FE psychosis 70 controls	1 - 2.5	<b>Improvement</b> in schizophrenia, affective psychoses, and control subjects, with no significant group-by-time interactions

### **5.1.2 Studies without a healthy control group**

Virtually all studies that do not include a control group report stability or improvement in all neuropsychological domains for intervals of 1 to 4 years. The only exception is a study by Gold et al., (Gold *et al.*, 1999), whose patients worsened over time in motor speed (finger tapping). However, improvement over 5 years in intellectual abilities in patients with first episode psychosis reported by Gold et al., (Gold *et al.*, 1999) was attributed to neuroleptic treatment. Moreover, Gold (Gold, 2004) stated in his review that course of impairment in schizophrenia “is a stable, not a moving target” and relatively independent from symptoms.

Regarding the evolution of deficits over longer periods of time, two studies that investigated this question reported decline in neuropsychological performance. Stirling et al., (Stirling *et al.*, 2003) found decline in some tasks of visuospatial ability (object assembly, picture completion, and memory for designs) in patients after a mean follow-up period of 10 years. Oie et al., found decline in neuropsychological performance particularly in verbal memory, attention, and processing speed (Oie *et al.*, 2008). However, studies that do not include a healthy control group, although providing important information regarding the absolute time course of cognitive abilities in schizophrenia, are not informative regarding changes that might occur compared to healthy individuals, and thus do not take into account other factors that might affect performance, such as familiarity with the procedures and practice effects, or age-related cognitive changes. This is particularly evident in the above-mentioned study by Stirling et al., who did not account for the effects of aging in the statistical analyses but utilized comparisons to normative data (Stirling *et al.*, 2003). Unfortunately, normative data is frequently based on relatively small samples and includes ranges of ages which don't allow for an accurate assessment of the effects of age on cognitive tests

### **5.1.3 Studies with the presence of a healthy control group**

In studies that include a healthy control group, cognitive changes in patients for the most part parallel those observed in healthy control subjects. However, in some studies patients failed to improve as much as controls, or even deteriorated in some of the tasks used to assess performance. Studies investigating the course of neuropsychological deficits in first episode

patients relative to a healthy control groups differ along several dimensions, thus limiting the interpretability of results: For example, there are important differences among studies in patient sampling, with some studies (Albus *et al.*, 2002, Bilder *et al.*, 1991, Censits *et al.*, 1997) assessing only patients with schizophrenia, while others include patients with schizoaffective, schizophreniform and other psychotic disorders (Addington *et al.*, 2005, Hill *et al.*, 2004, Hoff *et al.*, 1999, Hoff *et al.*, 2005, Leeson *et al.*, 2009a, Leeson *et al.*, 2009b, Rodriguez-Sanchez *et al.*, 2008) or even patients with affective disorders with mood-incongruent delusions (Mayoral *et al.*, 2008). Other important methodological differences include: (1) patient recruitment strategies (inpatients versus inpatients and outpatients and the timing of baseline neuropsychological evaluation in patients (before initiation of treatment versus variable time into stabilization of symptoms, (2) duration of follow-up period from 1 to 13 years, as well as (3) differences in the specific neuropsychological measures implemented, their categorization, and their use in statistical analyses. For example, Mayoral *et al.*, included measures of verbal fluency in their composite measure of executive function, whereas most other studies assess verbal fluency separately (Mayoral *et al.*, 2008) [for example:(Addington *et al.*, 2005, Albus *et al.*, 2006)], or as a part of a composite measure of language ability [for example (Censits *et al.*, 1997, Hoff *et al.*, 1999, Hoff *et al.*, 2005)]. Another potential source for variation in findings is differences in recruitment strategies for the healthy control subjects. Finally, an additional confounding factor is attrition rate, which ranges widely between studies, from 70 – 90% in some studies (Albus *et al.*, 2006, Albus *et al.*, 2002, Hill *et al.*, 2004, Mayoral *et al.*, 2008, Rodriguez-Sanchez *et al.*, 2008) to less than 50% in others (Addington *et al.*, 2005, Hoff *et al.*, 2005).

#### **5.1.4 Studies with first episode, early onset and chronic patients**

Most studies examining neurocognitive deficits in psychosis have involved chronic patients (Bilder *et al.*, 2002, Harvey *et al.*, 1997, Mohamed *et al.*, 1999, Nuechterlein, 1985) and the results may reflect the long-term illness and/or exposure to treatment. Overall severity of the deficit is about 0.3 to 1.0 standard deviations greater in the groups of chronic patients compared to first-episode patients (Bilder *et al.*, 1992, Hoff *et al.*, 1998). It remains unclear whether this discrepancy reflects sampling bias (i.e., many first-episode patients will not go on to have chronic illness) or a deteriorating course and associated cognitive decline in some patients.

Longitudinal studies of first onset of psychosis patients are of special relevance when it comes to evaluating the course of cognition in schizophrenia since they provide an adequate and realistic baseline measure of cognitive performance. Most of the previous studies in first onset of schizophrenia have described stability or improvement in cognitive functioning over time (Censits *et al.*, 1997, Gold *et al.*, 1999, Hill *et al.*, 2004, Hoff *et al.*, 1999, Hoff *et al.*, 2005, Nopoulos *et al.*, 1994, Sweeney *et al.*, 1991). In contrast, Stirling *et al.* (Stirling *et al.*, 2003) and Øie *et al.*, (Oie *et al.*, 2008) reported a progressive cognitive deterioration. Nevertheless, follow-up investigations of cognition in chronic schizophrenia have shown a marked deterioration over time (Harvey *et al.*, 1999b, Morrison *et al.*, 2006, Waddington and Youssef, 1996). Some of the cross sectional studies, but not all (Goldberg *et al.*, 1993, Hyde *et al.*, 1994) have also suggested that the duration of illness was positively associated with greater cognitive deficits, thus supporting the notion of a progressive cognitive decline in schizophrenia (Bilder *et al.*, 1992, Heaton *et al.*, 1994). However, Rund in a review of the literature, concluded that there is no significant progressive cognitive impairment in schizophrenia (Rund, 1998).

Several methodological limitations (small sample size, lack of cognitive longitudinal assessments in the control group, previously treated patients) might contribute to inconsistent results. Kurtz *et al.*, update on neurocognitive impairments across the lifespan in schizophrenia revealed that in outpatient groups (age range from 20-65 years) overall cognitive dysfunctions remain stable and no further deterioration was present. In particular, full scale IQ, attention, memory, verbal and visual skills remained remarkably stable over time (Kurtz *et al.*, 2005). The existence of longitudinal comparison samples of healthy volunteers is of special relevance when considering the effects of repeated exposure to cognitive tests (practice effect) and thus interpreting the results of longitudinal investigations. Cervellione *et al.*, followed a sample of 26 early onset schizophrenia and 26 healthy controls 13 months after baseline assessment (Cervellione *et al.*, 2007). Statistics from this study have shown relatively stable course of cognitive dysfunctions despite changes in clinical status. Frangou *et al.*, examined cognitive function over a mean interval of 4 years in 20 adolescents with schizophrenia (Frangou *et al.*, 2008). They found that most aspects of cognitive function remain relatively stable in early onset schizophrenia patients during adolescence; there was evidence for deterioration in immediate verbal memory and attention while speed of information processing show improvement.

The existing literature does not provide an adequate answer to the question of the course of cognitive impairment in psychosis. The majority of studies suggest that neuropsychological deficits that are present following a first episode of psychosis remain stable over time (Bozikas and Andreou, 2011, Hoff *et al.*, 1999, Hoff *et al.*, 2005, Leeson *et al.*, 2009a, Leeson *et al.*, 2009b, Nopoulos *et al.*, 1994, Rund, 1998, Sweeney *et al.*, 1991). These findings support the view of schizophrenia as a static encephalopathy. In this view schizophrenia is associated with neuropsychological impairment that begins at the time of or even before onset of psychopathological symptoms and remains stable over time even during symptom free periods (Bozikas and Andreou, 2011, Hoff *et al.*, 1999, Leeson *et al.*, 2009a, Leeson *et al.*, 2009b, Nopoulos *et al.*, 1994, Rund, 1998, Rund *et al.*, 2007, Sweeney *et al.*, 1991).

Nevertheless, other studies provide support for the view of schizophrenia as a degenerative neuropsychiatric disorder. This is characterised by onset in young adulthood followed by a length period of gradual cognitive decline. This view is supported by studies using MRI (Mathalon *et al.*, 2001), in studies including patients with late-life schizophrenia (Fucetola *et al.*, 2000, Harvey *et al.*, 1999a, Harvey *et al.*, 1999b), as well as in studies showing changes over time in specific cognitive functions [e.g., (Bilder *et al.*, 1991).]

This evidence on stability in neuropsychological performance is consistent with Kurtz (Kurtz *et al.*, 2005) investigation on neurocognitive impairments across the lifespan in schizophrenia. The study revealed that in outpatients group (age range from 20-65years) overall cognitive dysfunctions remain stable and no further deterioration is present. In particular, full scale IQ, attention, memory, verbal and visual skills remained remarkably stable over time. With regards to other psychosis group, Pavuluri *et al.*, reported that cognitive trajectory is stable over time in children diagnosed with bipolar disorder (Pavuluri *et al.*, 2009). Research yielded that adults and older adults also show stable course of cognition over 1-3 year interval (Depp *et al.*, 2008, Mur *et al.*, 2008). Yet, no evidence for decline in bipolar patients has been published. Further to cognitive stabilization, Heaton *et al.*, published one of the first largest multi-year follow-up study including a large sample of 142 schizophrenia outpatients and 206 controls (Heaton *et al.*, 2001). He reported no decline after 5 years interval. No significant differences in neuropsychological change were

found between schizophrenic subgroups defined by current age, age at onset of illness, baseline level of neuropsychological impairment, improvement or worsening of clinical symptoms, and occurrence of incident tardive dyskinesia. Norms for change also failed to show neuropsychological progression in individuals with schizophrenia. Heaton (Heaton *et al.*, 2001) also pointed out that neuropsychological impairment in ambulatory persons with schizophrenia appears to remain stable, regardless of baseline characteristics and changes in clinical state.

The main outcome of the literature review is that cognitive deficits are relatively stable over long periods after onset of schizophrenia. If any change occurs, it is more often an improvement in neuropsychological performance. Some neuropsychological functions were reported to improve in first episode patients during the first stage of illness (Hoff *et al.*, 1992, Nopoulos *et al.*, 1994, Sweeney *et al.*, 1991). Furthermore, Szoke *et al.*, carried out a meta-analysis of 53 longitudinal studies of cognitive performance in schizophrenia (Szoke *et al.*, 2008). Results indicated a significant improvement in most cognitive domains in the course of antipsychotic treatment. However this was attributed to practice-effects. Also, stability in performance on semantic verbal fluency in both schizophrenic and healthy controls was observed. Szoke *et al.*, proposed that semantic verbal fluency (category) may be a possible cognitive endophenotype in schizophrenia disorder (Szoke *et al.*, 2008). In other words, verbal fluency impairment is suggested to be a heritable state-dependant characteristic of schizophrenia disorder (a genetic biomarker of schizophrenia). This is in line with a number of studies that reported high level of verbal fluency deficit in both schizophrenia patients and first-degree relatives of those patients (Snitz *et al.*, 2006, Szoke *et al.*, 2008).

#### **5.1.4 Aims and objectives**

The aim of this section of the thesis is to characterize the trajectory of cognitive functioning along the course of the psychotic illness. We examined the following three questions:

- 4) What is the trajectory of the cognitive impairment seen in psychosis after the first psychotic episode?
- 5) Do all neuropsychological deficits follow the same trajectory?
- 6) Do different psychotic disorders present the same trajectory of cognitive functioning?

## **5.2 Materials and methods**

### **5.2.1 Follow-up study cohort**

The mean time of follow-up was 104.2 months (SD=28.84) for patients (N=108) and 102.32 (SD=30.03) for the comparison group (N=103). Fifty five subjects in the follow-up sample of 108 patients met ICD-10 (1992) diagnostic criteria for schizophrenia, and an additional nine met ICD-10 diagnostic criteria for schizoaffective disorder. Nineteen met diagnostic criteria for bipolar/manic, fourteen for depressive psychosis and eleven for other psychosis.

#### **5.2.1.1 Cases**

When recruited to the baseline study, participants provided detailed contact details for themselves, their GP's and their relatives, and gave consent to be contacted for follow-up. At time of follow-up, we wrote to all participants, inviting them to take part in this follow-up study, or made contact with them via a care co-ordinator, if in contact with services. A reply slip was enclosed, for participants to indicate whether or not they would take part, or require further information. Those from whom no reply was received were called by telephone in order to make initial contact, and thereafter non-responders were sent 2 further invitations at one-month intervals. Where it was not been possible to obtain a telephone number for the participant, we would call at their address, if they had not contacted us after 2 weeks. A minority had moved residence in the intervening years, and those participants were traced through contact with their GP/consultant psychiatrist or, if necessary, via the relevant Primary Care Trust. For difficult-to-trace participants or for death certificates of those who died during the follow-up period, both the National Strategic Tracing Service Website (<https://nwww.nsts.nhs.uk>) and the Office of National Statistic (ONS) were applied to in order to trace participant.

#### *Clinical evaluation and diagnosis*

At follow-up, clinical information were obtained through various sources: participant interview, casenote review and informant interview. The casenote review involved a detailed review of the medical and nursing case records of all the cases (both interviewed and non-interviewed) to supplement information obtained at interview. Information derived from several sources was

deemed to be superior to that from only one source. Instances in which patient interview was achieved are hereafter referred to as 'patient interview' instances in which interviews were possible with neither the participant nor an informant are denoted 'casenotes only'.

Information on illness course was obtained using an amended version of the WHO Life Chart (World Health Organization., 1994). This measure has been used successfully in previous long-term follow-up studies, and has been shown to be reliable in the assessment of clinical ratings (Susser *et al.*, 2000). Presence or absence of psychotic symptoms during the follow-up period was established with the SCAN (World Health Organization., 1994), in accordance with the WHO and other long-term outcome studies (Jablensky *et al.*, 1992). In addition, the Positive and Negative Syndrome Scale (Kay *et al.*, 1989) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982) were used to assess presence and severity of current positive and negative symptoms of psychosis.

For each participant a lifetime diagnosis according to ICD-10 (World Health Organisation, 1992) and DSM-IV (American Psychiatric Association, 2000) criteria was formulated in consensus meetings with senior clinicians and academics where information from all the sources described above were considered and reviewed, blind to subject age, ethnicity, treatment, and baseline diagnosis. These diagnoses were used for the present analysis.

#### **5.2.1.2 Healthy controls**

When recruited originally during the AESOP study, participants provided contact details for themselves. We wrote to all healthy volunteers, inviting them to take part in this follow-up study. A reply slip was enclosed, for participants to indicate whether or not they would take part, or require further information. If no reply to this was received after 2 weeks, then letters were followed up, wherever possible, with a telephone call until initial contact was established. Where it had not been possible to obtain a telephone number for the participant, we would call at their address (including morning, afternoon or evening visit) if they had not contacted us after 4 weeks.



The derivation of the follow-up sample included in the analysis reported here is presented in

**Figure 5.2** The analytic follow-up cohort comprised of 108 patients and 103 controls.

**Figure 5.2** The analytic cohort – follow-up study

<b>AESOP Follow-up Cohort</b>		
	<b>Cases</b>	<b>Controls</b>
<b>Eligible</b>	592	412
<b>Non-Participants (refused or could not be contacted or spoke no English)</b>	202 ← ↓	↓
<b>Consented</b>	390	412
<b>Incomplete or no neuropsychological testing</b>	145 ← ↓	↓ → 148
<b>Complete Neuropsychological Testing</b>	245	264
<b>Excluded:</b> <ul style="list-style-type: none"> <li>• Poor English speakers – Likely to affect neuropsychological tests</li> <li>• Missing data on more than three neuropsychological measures</li> <li>• Diagnosis of schizoaffective disorder – Too small for meaningful analysis</li> </ul>	58 ← ↓	↓ → 87
<b>Remaining in Analytic Cohort at baseline</b>	187	177
<b>Lost to follow-up:</b> <ul style="list-style-type: none"> <li>• Non responders (untraceable)</li> <li>• Refused</li> <li>• Deceased</li> <li>• Abroad</li> </ul>	79 ← ↓	↓ → 74
<b>Cohort at the follow-up</b>	108	103

### 5.2.2 Neuropsychological assessment

All participants underwent a battery of neuropsychological tests assessing general intellectual ability (IQ) as well as additional specific cognitive domains: (1) Learning and Memory (verbal and visual); (2) Executive functions and working memory; (3) Attention, concentration and mental speed; (4) Language; and (5) Visual constructual/perceptual abilities.

Full-scale IQ was derived from the WAIS-R (Wechsler, 1981) subtests Vocabulary, Comprehension, Digit Symbol Coding and Block Design. Verbal and Performance IQ were computed based on the relevant sub tests. Scoring followed standard procedures. Premorbid intelligence was estimated using the National Adult Reading Test (NART) (Nelson and Willison, 1991).

Specific cognitive domains were assessed using the following tests:

1. **Learning and memory: verbal** ( *short-term verbal immediate recall and delayed verbal recall*) were assessed using trials 1–5, 6 and 7, respectively, of the Rey Auditory Verbal Learning Test (RAVLT) and **visual** ( *immediate and delayed recall*) was examined using Visual Reproduction of the Wechsler Memory Scale - Revised (WMS-R) (Wechsler, 1987).
2. **Executive functions and working memory** were evaluated using the Trail Making Test - part B, Letter-Number Span, and Sets AB and B of Raven's Coloured Progressive Matrices (CPM)
3. **Attention, concentration and mental speed** were measured using Trail Making - part A and the WAIS-R Digit Symbol subtest.
4. **Language** was evaluated using the Semantic Fluency (categories 'body parts', 'fruits' and 'animals'), and Letter Fluency (letters F, A, S).

5. **Visual-construction/perceptual abilities** were assessed using set A of Raven's Coloured Progressive Matrices.

(Full description; please see chapter 3.2.4 Neuropsychological assessment).

### 5.2.3 Statistical analysis

Demographic and clinical characteristics of the baseline and follow up subgroups were compared using t-test and chi-square tests. Generalized Linear Mixed-Model Regression models were used to test the deterioration, static, lag and improvement hypotheses. Generalized Linear Mixed-Model Regression allows to maximise the use of the longitudinal nature of our data, as this technique permits the inclusion of multiple measurements per person, and irregular intervals between measurements, thereby increasing statistical power while controlling for within-individual variation. The effects of interest in the Generalized Linear Mixed-Model were the group main effect and the interaction between group and age (time). Age (time) was included as a main effect in all models but was not the effect of interest. Splines were used to model age effects (i.e., time) on cognition. A spline model estimates the response relation without assuming that the data follow a particular form, such as linear or cubic. This allows for an evaluation of the functional form of associations, and characterization of risk pattern including points of non-linearity (threshold effects). Ethnicity, years of education and gender were used as confounders in all models. Our primary analysis focused on general intellectual ability (IQ). Significance level was set at  $p=0.05$  (two-sided). All analyses were done using SAS version 9.3.

The *static deficit* hypothesis predicts static cognitive impairment, which is manifest in early-emerging cognitive deficits that remain stable. In generalized linear models with splines, this course is characterized by statistically significant group differences between cases and controls, but no statistically significant group by time interaction. The splines modelling the contrast between cases and controls will appear straight or with only minimal curving (**Figure 5.1**). The *deterioration* hypothesis predicts premorbid decline in cognitive performance. In generalized linear models with splines this course is characterized by statistically significant group by time

interaction. The spline modelling the contrast between cases and controls is characterized by a negative slope, or curving indicating an inverted-J shape (**Figure 5.1**). The *lag and amelioration* hypotheses predict slower or faster cognitive development relative to controls. In generalized linear models with splines this course is characterized by statistically significant group by time interaction. The spline modelling the contrast between cases and controls is characterized by a positive slope, or curving indicating J-shape (**Figure 5.1**). To test these hypotheses, I examined the statistical significance of the interaction and the direction of the splines that model the contrast between the diagnostic groups and controls for each cognitive function.

## 5.3 Results

### 5.3.1 Characteristics of cohort

#### 5.3.1.1 Representativeness

**Table 5.2** shows characteristics of the original cohort at baseline and of the follow up subsample. Follow-up neuropsychological evaluations were completed on 108 patients (65 males and 43 females) who were of 28.24 years old ( $SD= 9.9$ ) at baseline and 37.38 ( $SD= 10.38$ ) at follow-up, and 103 comparison subjects (45 males and 58 females) who were 35.99 years old ( $SD=10.87$ ) at baseline and 44.57 ( $SD=11.36$ ) at follow-up. There were no statistically significant differences between the subsamples of patients and controls that were followed-up and the original baseline cohorts in age [patients  $t(293)=1.13$ ,  $p=0.258$ ; controls  $t(277)=0.82$ ,  $p=0.408$ ], gender [patients  $\chi^2_{(1)} = 1.06$ ,  $p=0.303$ ; controls  $\chi^2_{(1)}=0.00$ ,  $p=0.992$ ], premorbid intellectual functioning [patients  $t(293)=0.11$ ,  $p=0.908$ ; controls  $t(277)=-1.64$ ,  $p=0.102$ ] and current IQ score [patients  $t(293)=0.46$ ,  $p=0.647$ ; controls  $t(277)=-1.68$ ,  $p=0.093$ ]. There were statistically significant differences between the subsamples of controls and the baseline cohort in ethnicity [ $\chi^2_{(1)} = 15.64$ ,  $p=0.001$ ] and in years of education [ $\chi^2_{(2)} = 12.45$ ,  $p=0.002$ ] but not in the subsamples of patients [ethnicity:  $\chi^2_{(1)} = 0.00$ ,  $p=0.994$ ; patients years of education:  $\chi^2_{(2)} = 2.32$ ,  $p=0.314$ ]. Overall, the patients from the original cohort at baseline were similar to those in the follow up in terms of the demographic variables. This similarity suggests that the follow up cohort is a representative sample of the original cohort at baseline.

**Table 5.2 Characteristics of the original cohort at baseline and follow-up**

Original cohort					Follow-up cohort							
	Characteristics at baseline				Characteristics at baseline				Characteristics at follow-up			
	Patients (N= 187)		Controls (N = 176)		Patients (N= 108)		Controls (N= 103)		Patients (N = 108)		Controls (N = 103)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<b>Age</b>	29.64	10.41	37.24	12.87	28.24	9.90	35.99	10.87	37.38	10.38	44.57	11.36
	N	%	N	%	N	%	N	%				
<b>Gender (Male)</b>	101	54.0	77	43.8	65	60.2	45	43.7	--		--	
<b>Ethnicity (White)</b>	109	59.0	113	64.4	63	58.9	41	39.8	--		--	
<b>Years of Education</b>												
11 ( <i>compulsory</i> )	123	64.4	84	47.7	66	62.0	38	36.9	--		--	
12-13 ( <i>post-compulsory</i> )	40	21.5	52	29.5	21	19.0	21	20.4	--		--	
14 or more ( <i>college, graduate or post-graduate</i> )	24	14.1	40	22.8	21	19.0	44	42.7	--		--	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<b>Estimated premorbid IQ</b>	99.36	13.24	106.3	12.63	99.17	14.54	108.85	12.39	102.10	15.12	107.52	15.73
<b>Current IQ</b>	92.40	16.59	102.93	15.15	91.46	17.58	106.19	16.43	89.75	16.31	105.91	15.23

Patients: age  $t(293) = 1.13$ ,  $p=0.258$ ; Controls age:  $t(277) = 0.82$ ,  $p=0.408$

Patients gender: chi-square (1) = 1.06,  $p=0.303$ ; Controls gender: chi-square (1) = 0.00,  $p=0.992$

Patients ethnicity: chi-square (1) = 0.00,  $p=0.994$ ; Controls ethnicity: chi-square (1) = 15.64,  $p=0.001$

Patients years of education: chi-square (2) = 2.32,  $p=0.314$ ; Controls years of education: chi-square (2) = 12.45,  $p=0.002$

Patients: premorbid IQ  $t(293) = 0.11$ ,  $p=0.908$ ; Controls premorbid IQ:  $t(277) = -1.64$ ,  $p=0.102$

Patients: current IQ  $t(293) = 0.46$ ,  $p=0.647$ ; Controls current IQ:  $t(277) = -1.68$ ,  $p=0.093$

### 5.3.2 General intellectual ability

#### Deterioration hypothesis

There was evidence for cognitive deterioration among schizophrenia and bipolar/mania patients (**Figure 5.3 and Figure 5.5**). Examination of the splines demonstrated that schizophrenia and bipolar/mania patients had worsening performance on full scale IQ, and in particular on verbal IQ over time ( $p=0.02$  and  $p=0.014$  for time by group interaction for schizophrenia and bipolar/mania, respectively). Deterioration began in late adolescence and continued progressively until the 4<sup>th</sup> decade of life, after which performance levelled off with an impairment of approximately 1 SD.

#### Static hypothesis

Schizophrenia and bipolar/mania patients exhibited static cognitive deficits on performance IQ (**Figure 5.4**). A similar pattern was also apparent among patients with depressive psychosis. Analyses showed that these groups had lower scores than healthy comparison controls but the difference between patients and controls did not change over time, indicating that their impairment in performance IQ emerged by late adolescence and remained steady throughout adult life.

#### Lag and amelioration hypotheses

None of the groups showed a course consistent with the characteristics of the lag or amelioration hypotheses.

### 5.3.3 Specific cognitive functions

#### Deterioration hypothesis

There was evidence supporting cognitive deterioration among schizophrenia patients on neuropsychological measures assessing specific processes of memory (Immediate Recall) and reasoning (Raven's Coloured Progressive Matrices set AB) (**Figure 5.9**). Deterioration on the Raven's Coloured Progressive Matrices set AB began later in life. Cognitive deterioration was

also evident on the category fluency and Trails Making Test Part A, with a similar pattern of deterioration later in life. These effects were only significant at trend level ( $p=0.067$  and  $p=0.074$ , respectively) (**Figure 5.8 and 5.7**). Deterioration on specific memory processes was also evident in bipolar/mania patients (**Figure 5.6**), and in patients with other psychoses (**Figure 5.6**). There was evidence for deterioration of bipolar/mania patients in verbal learning (**Figure 5.6**), yet the group x time interaction was not statistically significant ( $p=0.081$ ). In patients with other psychoses deterioration began later in life (**Figure 5.6**) ( $p=0.007$  for verbal learning,  $p=0.10$  for immediate recall,  $p=0.0075$  for delayed recall,  $p=0.088$  for visual memory).

#### Static hypothesis

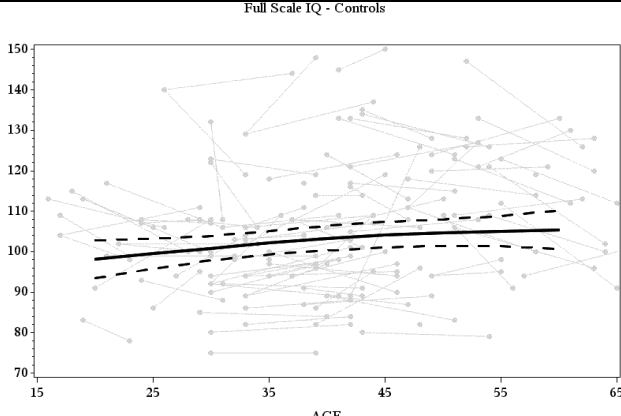
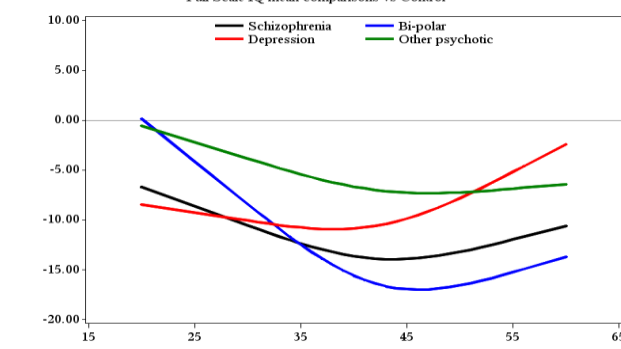
Static deficits were the dominant course evident in schizophrenia on specific cognitive functions, and were observed for verbal learning and delayed recall (**Figure 5.6**), digit symbol coding (**Figure 5.7**), letter fluency (**Figure 5.8**), Trail Making Test Part B, Letter-Number Span (**Figure 5.9**), and Raven's Coloured Progressive Matrices set A and set B (**Figure 5.10 and 5.9**). Static deficits were observed in bipolar/mania for Trail Making Test Part A, digit symbol coding (**Figure 5.7**), category fluency (**Figure 5.8**) and Raven's Coloured Progressive Matrices set A (**Figure 5.10**). Static deficits were observed in depressive psychosis for Trail Making Test Part A (**Figure 5.7**), Trail Making Test Part B, and Letter-Number Span (**Figure 5.9**).

#### Lag and amelioration hypotheses

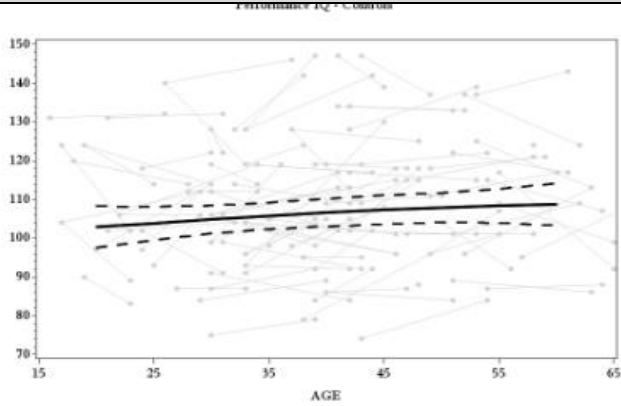
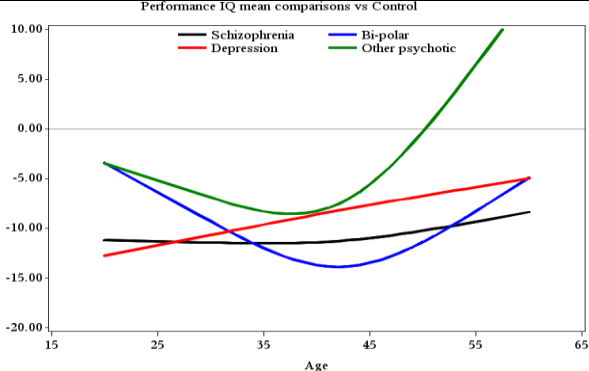
A frequent course in the depressive psychosis group was of later-life amelioration. Deficits worsened in the 3<sup>rd</sup> to 4<sup>th</sup> decades of life but performance improved thereafter. This was observed for verbal learning, immediate recall, delayed recall (**Figure 5.5**), digit symbol coding (**Figure 5.7**), letter fluency (**Figure 5.8**), and Raven's Coloured Progressive Matrices set B (**Figure 5.9**). The other psychoses group demonstrated a course characterized by amelioration on the Trail Making Test Part A (**Figure 5.7**).



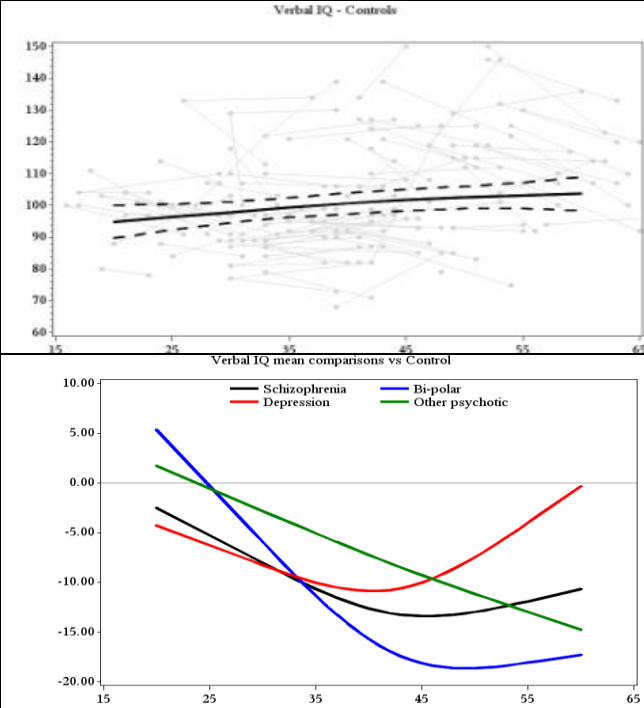
**Figure 5.3 IQ scores by age in healthy comparison subjects and patients with schizophrenia, bipolar/mania, depressive psychosis and other psychoses. Top figure illustrates individual trajectories and overall group trajectory in healthy comparison subjects. Lower figure shows non-standardised differences between patients groups and healthy comparison subjects based on splines. Presented are also corresponding t-test and significance values from the generalised linear mixed model regression for the group and age by group interaction**

Cognitive measures	Group comparison	Test for course
<b>Full scale IQ</b>		
	Schizophrenia vs. Controls	Group $t=6.33, p<0.0001$ Time X Group $t=1.95, p=0.062$
	Bipolar/Mania vs. Controls	Group $t=4.46, p=0.0002$ Time X Group $t=2.30, p=0.029$
	Depressive Psychosis vs. Controls	Group $t=3.31, p=0.0031$ Time X Group $t=0.46, p=0.65$
	Other psychoses vs. Controls	Group $t=2.22, p=0.036$ Time X Group $t=0.91, p=0.36$

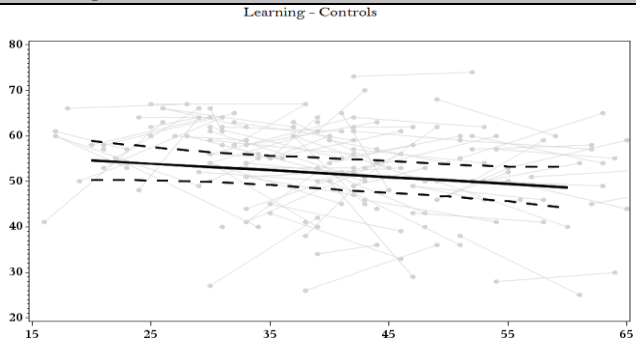
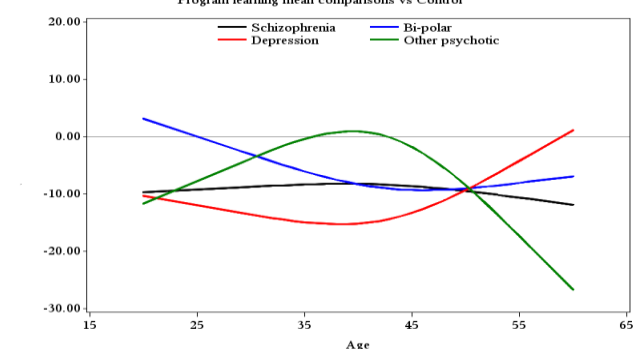
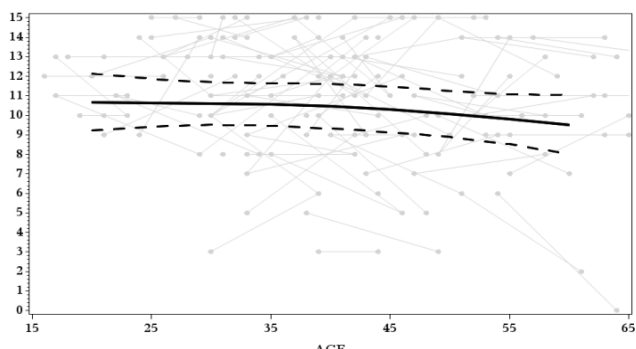
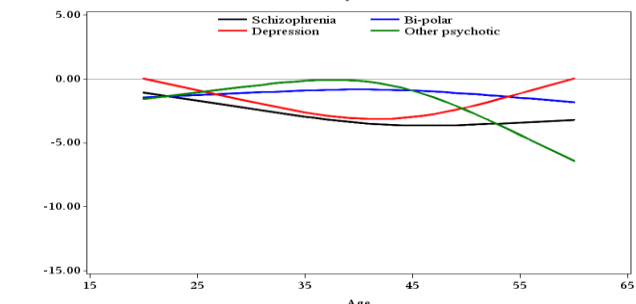
**Figure 5.4 Performance IQ scores by age in healthy comparison subjects and patients with schizophrenia, bipolar/mania, depressive psychosis and other psychoses. Top figure illustrates individual trajectories and overall group trajectory in healthy comparison subjects. Lower figure shows non-standardised differences between patients groups and healthy comparison subjects based on splines. Presented are also corresponding t-test and significance values from the generalised linear mixed model regression for the group and age by group interaction**

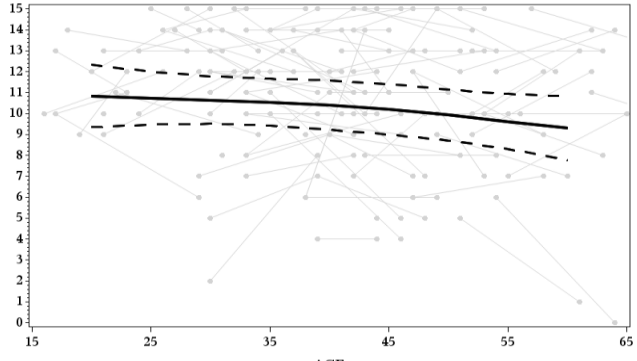
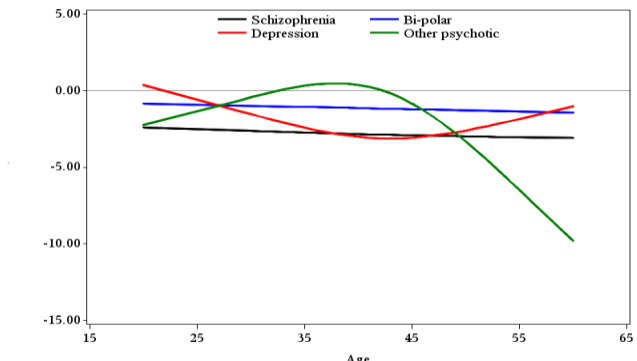
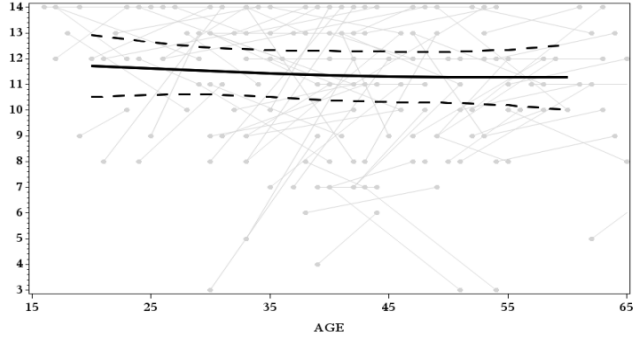
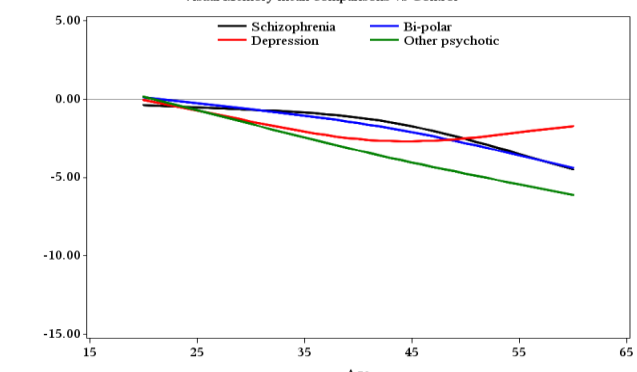
Cognitive measures	Group comparison	Test for course
<b>Performance IQ</b>		
	Schizophrenia vs. Controls	Group $t=5.77, p<0.0001$ Time X Group $t=0.11, p=0.91$
	Bipolar/Mania vs. Controls	Group $t=3.56, p=0.0017$ Time X Group $t=1.44, p=0.16$
	Depressive Psychosis vs. Controls	Group $t=3.16, p=0.004$ Time X Group $t=0.04, p=0.96$
	Other psychoses vs. Controls	Group $t=2.15, p=0.042$ Time X Group $t=0.87, p=0.39$

**Figure 5.5 Verbal IQ scores by age in healthy comparison subjects and patients with schizophrenia, bipolar/mania, depressive psychosis and other psychoses. Top figure illustrates individual trajectories and overall group trajectory in healthy comparison subjects. Lower figure shows non-standardised differences between patients groups and healthy comparison subjects based on splines. Presented are also corresponding t-test and significance values from the generalised linear mixed model regression for the group and age by group interaction**

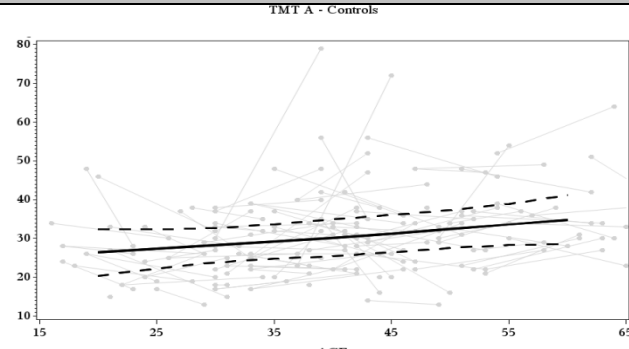
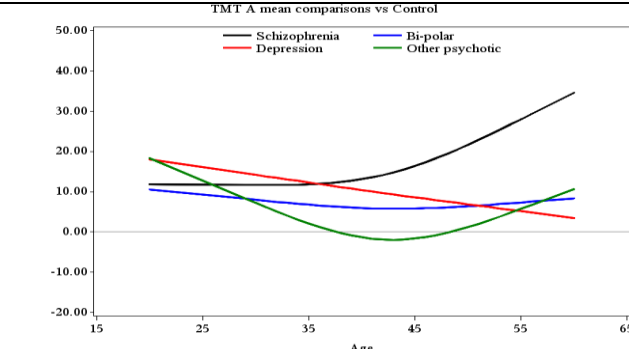
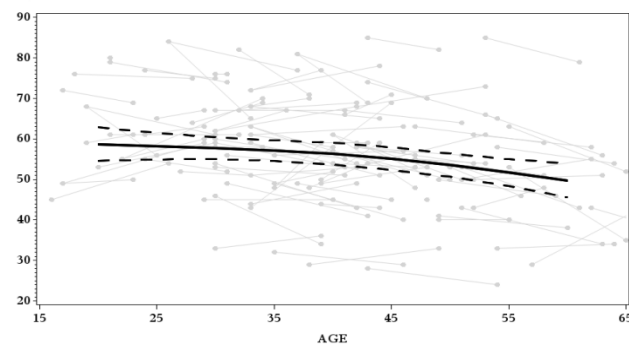
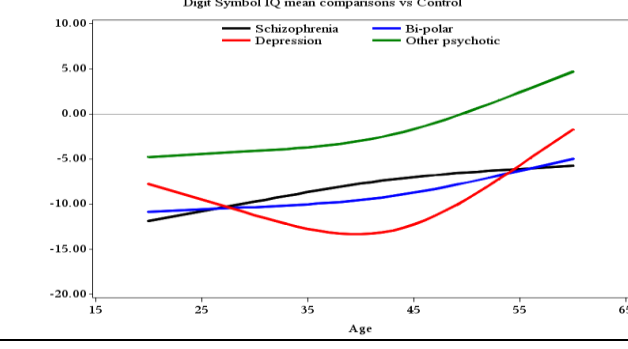
Cognitive measures	Group comparison	Test for course
<b>Verbal IQ</b>		
	Schizophrenia vs. Controls	Group $t=4.94, p<0.0001$ Time X Group $t=2.42, p=0.02$
	Bipolar/Mania vs. Controls	Group $t=3.77, p=0.001$ Time X Group $t=2.60, p=0.014$
	Depressive Psychosis vs. Controls	Group $t=2.33, p=0.028$ Time X Group $t=0.95, p=0.34$
	Other psychoses vs. Controls	Group $t=1.95, p=0.062$ Time X Group $t=1.07, p=0.29$

**Figure 5.6 Learning and Memory tests scores by age in healthy comparison subjects and patients with schizophrenia, bipolar/mania, depressive psychosis and other psychoses.** Top figure illustrates individual trajectories and overall group trajectory in healthy comparison subjects. Lower figure shows non-standardised differences between patients groups and healthy comparison subjects based on splines. Presented are also corresponding t-test and significance values from the generalised linear mixed model regression for the group and age by group interaction.

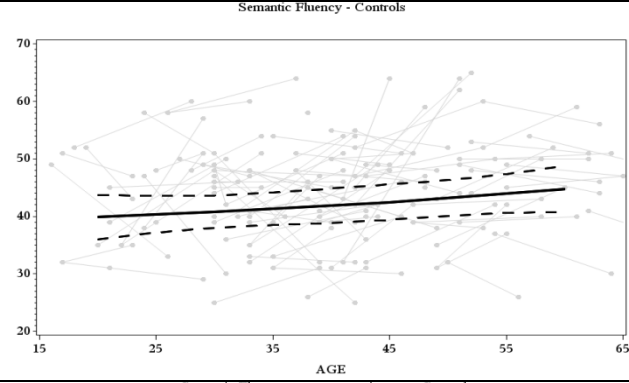
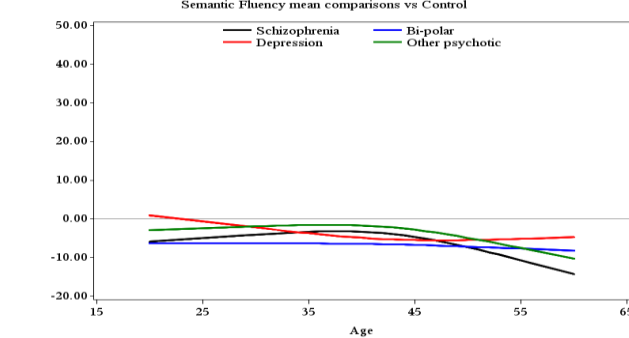
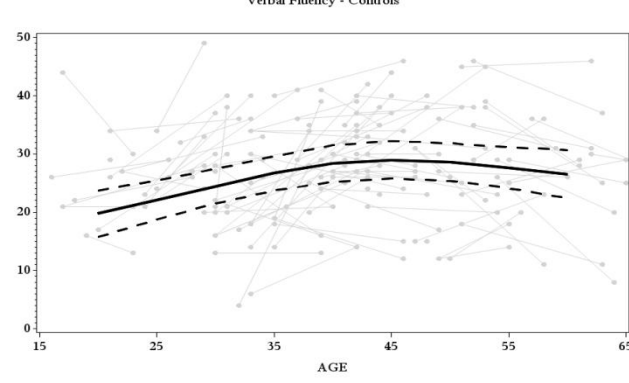
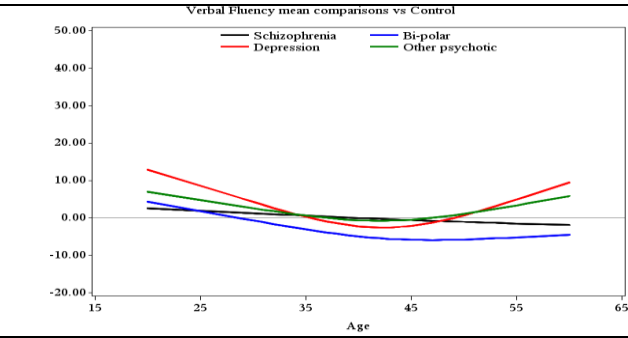
Learning and Memory	Group comparison	Test for course
<b>Learning</b>		
	Schizophrenia vs. Controls	Group $t=4.95, p<0.0001$ Time X Group $t=0.55, p=0.58$
	Bipolar/Mania vs. Controls	Group $t=1.94, p=0.065$ Time X Group $t=1.81, p=0.081$
	Depressive Psychosis vs. Controls	Group $t=4.31, p=0.0003$ Time X Group $t=2.46, p=0.021$
	Other psychoses vs. Controls	Group $t=2.00, p=0.057$ Time X Group $t=2.94, p=0.007$
<b>Immediate Recall</b>		
	Schizophrenia vs. Controls	Group $t=4.04, p=0.0005$ Time X Group $t=2.24, p=0.034$
	Bipolar/Mania vs. Controls	Group $t=1.25, p=0.22$ Time X Group $t=0.33, p=0.74$
	Depressive Psychosis vs. Controls	Group $t=1.77, p=0.09$ Time X Group $t=2.18, p=0.039$
	Other psychoses vs. Controls	Group $t=1.02, p=0.031$ Time X Group $t=1.66, p=0.10$

Learning and Memory (cont.)	Group comparison	Test for course
<b>Delayed Recall</b>		
	Schizophrenia vs. Controls	Group $t=4.45, p=0.0002$ Time X Group $t=0.41, p=0.68$
	Bipolar/Mania vs. Controls	Group $t=1.23, p=0.23$ Time X Group $t=0.14, p=0.89$
	Depressive Psychosis vs. Controls	Group $t=2.02, p=0.056$ Time X Group $t=1.94, p=0.064$
	Other psychoses vs. Controls	Group $t=1.29, p=0.21$ Time X Group <b><math>t=2.91, p=0.0075</math></b>
<b>Visual</b>		
	Schizophrenia vs. Controls	Group $t=1.68, p=0.11$ Time X Group $t=1.33, p=0.20$
	Bipolar/Mania vs. Controls	Group $t=1.98, p=0.065$ Time X Group $t=0.78, p=0.44$
	Depressive Psychosis vs. Controls	Group $t=2.03, p=0.06$ Time X Group $t=1.56, p=0.13$
	Other psychoses vs. Controls	Group $t=2.49, p=0.024$ Time X Group $t=1.81, p=0.088$

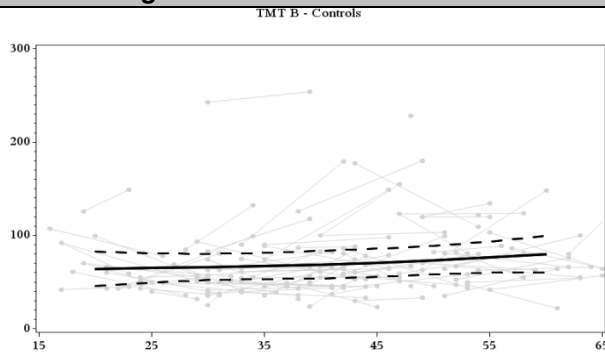
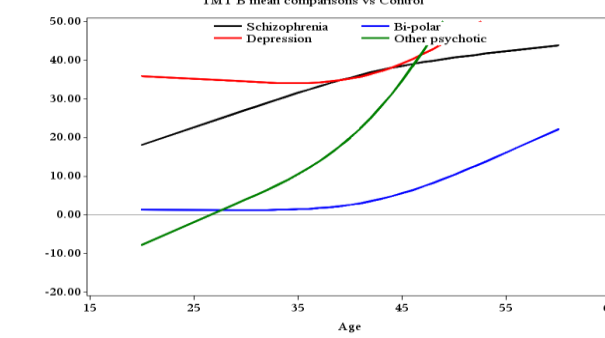
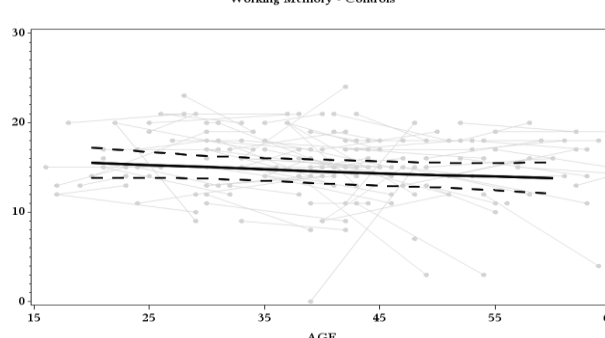
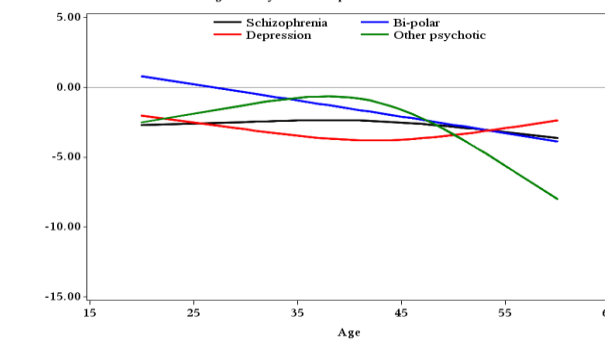
**Figure 5.7 Processing Speed tests scores by age in healthy comparison subjects and patients with schizophrenia, bipolar/mania, depressive psychosis and other psychoses.** Top figure illustrates individual trajectories and overall group trajectory in healthy comparison subjects. Lower figure shows non-standardised differences between patients groups and healthy comparison subjects based on splines. Presented are also corresponding t-test and significance values from the generalised linear mixed model regression for the group and age by group interaction.

Processing Speed	Group comparison	Test for course
<b>Trail Making Test Part A</b>		
	Schizophrenia vs. Controls	Group $t=5.19, p<0.0001$ Time X Group $t=1.86, p=0.074$
	Bipolar/Mania vs. Controls	Group $t=2.10, p=0.047$ Time X Group $t=0.48, p=0.63$
	Depressive Psychosis vs. Controls	Group $t=3.39, p=0.0028$ Time X Group $t=0.86, p=0.39$
	Other Psychoses vs. Controls	Group $t=1.61, p=0.12$ Time X Group $t=2.35, p=0.027$
<b>Digit Symbol</b>		
	Schizophrenia vs. Controls	Group $t=4.32, p=0.0003$ Time X Group $t=1.18, p=0.24$
	Bipolar/Mania vs. Controls	Group $t=3.54, p=0.0018$ Time X Group $t=0.11, p=0.91$
	Depressive Psychosis vs. Controls	Group $t=3.57, p=0.0016$ Time X Group $t=1.98, p=0.058$
	Other psychoses vs. Controls	Group $t=0.45, p=0.65$ Time X Group $t=0.19, p=0.85$

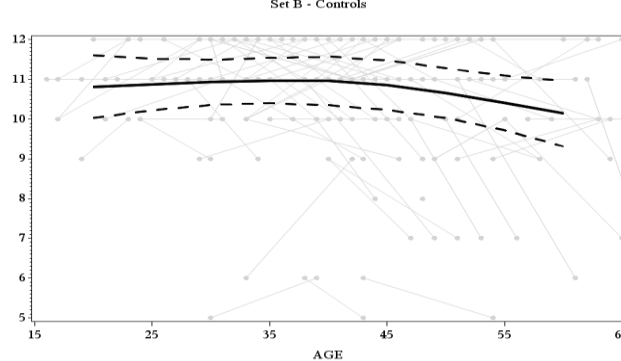
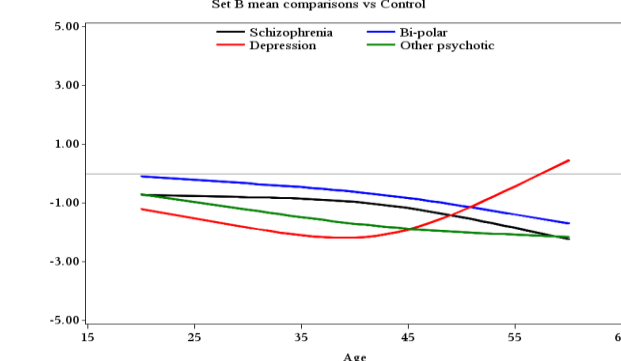
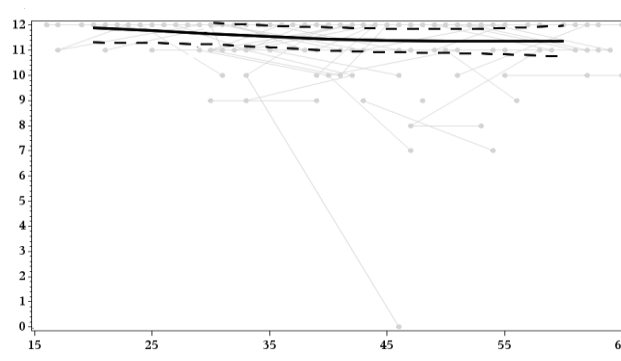
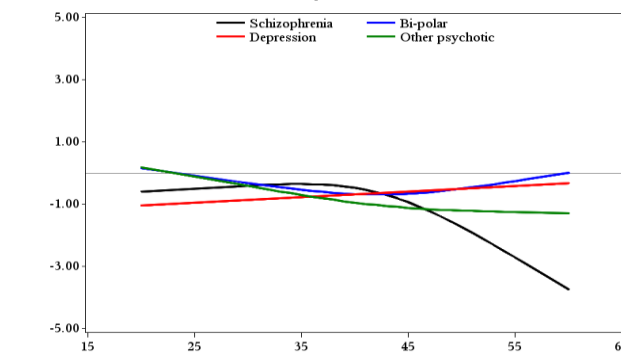
**Figure 5.8 Language tests scores by age in healthy comparison subjects and patients with schizophrenia, bipolar/mania, depressive psychosis and other psychoses. Top figure illustrates individual trajectories and overall group trajectory in healthy comparison subjects. Lower figure shows non-standardised differences between patients groups and healthy comparison subjects based on splines. Presented are also corresponding t-test and significance values from the generalised linear mixed model regression for the group and age by group interaction.**

Language	Group comparison	Test for course
<b>Category fluency</b>		
	Schizophrenia vs. Controls	Group $t=4.81, p=0.0001$ Time X Group $t=1.92, p=0.067$
	Bipolar/Mania vs. Controls	Group $t=3.74, p=0.001$ Time X Group $t=0.00, p=1.00$
	Depressive Psychosis vs. Controls	Group $t=1.88, p=0.075$ Time X Group $t=1.09, p=0.28$
	Other psychoses vs. Controls	Group $t=1.89, p=0.072$ Time X Group $t=0.31, p=0.75$
<b>Letter fluency</b>		
	Schizophrenia vs. Controls	Group $t=0.88, p=0.39$ Time X Group $t=0.79, p=0.43$
	Bipolar/Mania vs. Controls	Group $t=1.27, p=0.22$ Time X Group $t=1.59, p=0.12$
	Depressive Psychosis vs. Controls	Group $t=1.70, p=0.10$ Time X Group $t=3.28, p=0.003$
	Other psychoses vs. Controls	Group $t=0.28, p=0.78$ Time X Group $t=1.4, p=0.16$

**Figure 5.9 Executive Functions and Working Memory tests scores by age in healthy comparison subjects and patients with schizophrenia, bipolar/mania, depressive psychosis and other psychoses.** Top figure illustrates individual trajectories and overall group trajectory in healthy comparison subjects. Lower figure shows non-standardised differences between patients groups and healthy comparison subjects based on splines. Presented are also corresponding t-test and significance values from the generalised linear mixed model regression for the group and age by group interaction.

Executive Functions and Working Memory		Group comparison	Test for course
Trail Making Test Part B			
	Schizophrenia vs. Controls	Group t=3.50, p=0.0024 Time X Group t=1.25, p=0.22	
	Bipolar/Mania vs. Controls	Group t=0.24, p=0.81 Time X Group t=0.46, p=0.65	
	Depressive Psychosis vs. Controls	Group t=4.13, p=0.0006 Time X Group t=0.77, p=0.45	
	Other psychoses vs. Controls	Group t=0.70, p=0.49 Time X Group t=0.84, p=0.41	
Letter-Number Span			
	Schizophrenia vs. Controls	Group t=3.58, p=0.0018 Time X Group t=0.33, p=0.74	
	Bipolar/Mania vs. Controls	Group t=0.86, p=0.39 Time X Group t=0.83, p=0.41	
	Depressive Psychosis vs. Controls	Group t=3.09, p=0.0056 Time X Group t=0.82, p=0.41	
	Other psychoses vs. Controls	Group t=1.53, p=0.14 Time X Group t=1.63, p=0.11	



Executive Functions and Working Memory (cont.)		Group comparison	Test for course
RAVEN Set B			
	Schizophrenia vs. Controls	Group t=2.86, p=0.009 Time X Group t=0.76, p=0.45	
	Bipolar/Mania vs. Controls	Group t=1.15, p=0.26 Time X Group t=0.27, p=0.78	
	Depressive Psychosis vs. Controls	Group t=2.94, p=0.0075 Time X Group t=2.03, p=0.053	
	Other psychoses vs. Controls	Group t=2.65, p=0.014 Time X Group t=0.77, p=0.44	
RAVEN Set AB			
	Schizophrenia vs. Controls	Group t=2.27, p=0.033 Time X Group t=3.41, p=0.0023	
	Bipolar/Mania vs. Controls	Group t=1.20, p=0.24 Time X Group t=0.93, p=0.36	
	Depressive Psychosis vs. Controls	Group t=1.86, p=0.076 Time X Group t=0.39, p=0.69	
	Other psychoses vs. Controls	Group t=0.58, p=0.56 Time X Group t=1.23, p=0.22	

**Figure 5.10 Visuospatial test scores by age in healthy comparison subjects and patients with schizophrenia, bipolar/mania, depressive psychosis and other psychoses. Top figure illustrates individual trajectories and overall group trajectory in healthy comparison subjects. Lower figure shows non-standardised differences between patients groups and healthy comparison subjects based on splines. Presented are also corresponding t-test and significance values from the generalised linear mixed model regression for the group and age by group interaction**

Visuospatial	Group comparison	Test for course
<b>Raven Set A</b>		
	Schizophrenia vs. Controls	Group $t=1.77, p=0.091$ Time X Group $t=0.30, p=0.76$
	Bipolar/Mania vs. Controls	Group $t=1.99, p=0.058$ Time X Group $t=1.04, p=0.31$
	Depressive Psychosis vs. Controls	Group $t=1.30, p=0.20$ Time X Group $t=1.19, p=0.24$
	Other psychoses vs. Controls	Group $t=0.67, p=0.51$ Time X Group $t=0.93, p=0.36$

## 5.4 Discussion

Findings from this study strongly support the hypothesis that schizophrenia is characterized by cognitive decline in generalized cognitive ability, especially verbal IQ. Results also demonstrate that different cognitive functions appear to follow different courses. Cognitive decline appears to be present in verbal knowledge acquisition and memory and reasoning abilities. A static impairment appears to characterize processing speed, visuospatial, language and executive function/working memory abilities. Bipolar/Mania was also characterized by cognitive decline. In bipolar/mania cognitive decline was evident predominantly in verbal knowledge acquisition. A static impairment appears to characterize processing speed, language and visuospatial abilities in bipolar/mania.

While both schizophrenia and bipolar/mania cases showed cognitive decline beginning in late adolescence and continuing monotonically until the early 40's, schizophrenia patients already presented with a moderate impairment (approximately 0.5 standard deviation of impairment) in late adolescence. A recent meta analysis demonstrated that future schizophrenia patients have cognitive impairments in childhood and early adolescence which are of similar magnitude (Woodberry *et al.*, 2008). In contrast, bipolar/mania cases had normal performance at late adolescence. Normal premorbid cognitive functioning has been described in bipolar patients (Koenen *et al.*, 2009, Reichenberg *et al.*, 2010). Bipolar/mania ended up more than 1 standard deviation below normal controls.

In depressive psychosis patients a static impairment was evident in general intellectual ability and on specific cognitive measures. Interestingly there was a frequent course of later-life amelioration for processing speed, executive function, language and learning and memory. In patients with other psychoses there was no evidence for decline in general intellectual ability memory functions including verbal and visual presented with a deteriorating course that began later in life. A course of amelioration appears to apply to processing speed.

#### **5.4.1 What do the findings suggest regarding the aetiology of schizophrenia?**

The neurodevelopmental model of schizophrenia posits that there is insult to the brain acquired or inherited in early development. In line with this model, resulting cognitive deficits are manifested before the onset of psychotic symptoms and should remain static even during episodic-free phase (Weinberger, 1987). According to the neurodegenerative model, schizophrenia is characterised by onset in young adulthood followed by a lengthy period of gradual cognitive decline (Klingberg *et al.*, 2008). The existing literature does not provide adequate answers as to whether the trajectory of cognitive function over life is more consistent with a neurodevelopmental model of schizophrenia or a neurodegenerative pathogenesis.

The findings of the current study suggest that schizophrenia involves two processes: a neuropathology (Weinberger, 1987) fully developed early in adult life and which remains static throughout adult life affecting processing speed, visuospatial, language and executive function/working memory abilities, and a neurodegenerative pathogenesis affecting verbal knowledge acquisition and memory and reasoning abilities which begins in late adolescence or early adult life and continuous until the 4<sup>th</sup> decade of life.

#### **5.4.2 What do the findings suggest regarding the aetiology of Bipolar/Mania?**

The course of the generalized cognitive impairment in bipolar/mania patients was indistinguishable from that of schizophrenia patients. Deterioration was primarily evident in verbal knowledge acquisition. Static impairments were observed on measures of processing speed, language and visuospatial abilities. These findings suggest the aetiology of bipolar/mania also has origins in two interrelated processes: an early static one and neurodegenerative pathology. Models suggest partially shared aetiology between schizophrenia and bipolar disorder (Lichtenstein *et al.*, 2009), and neurodevelopmental aetiologies in bipolar disorder are still debated (Murray *et al.*, 2004). The present findings suggest that schizophrenia and bipolar mania share a neurodegenerative process but only schizophrenia presents with a neurodevelopmental one.

### **5.4.3 What do the findings suggest regarding the aetiology of depressive psychosis and other psychoses?**

The course of cognitive decline in patients with depressive psychosis was somewhat distinct from that of schizophrenia and bipolar/mania. Static deficits were the dominant course and were evident in general intellectual ability and in specific neuropsychological functions. Thus, the present findings suggest that a static model may be sufficient to describe the course of cognitive impairments in depressive psychosis.

In patients with other psychoses there was no evidence for deterioration in general intellectual ability. However, memory functions, both verbal and visual manifested a pattern of deterioration which happened later in life.

The findings should be interpreted in light of some limitations. The number of depressive psychosis and other psychoses case subjects was small, which had the practical effect of reducing the power to detect potentially meaningful group differences. Therefore, one should be cautious when interpreting the pattern of deficits in depressive and other psychotic disorders. To the best of my knowledge this is the first study reporting longitudinal cognitive outcome of these patient groups. When interpreting the different trajectories of cognitive performance across all diagnostic groups it should be acknowledged that certain abilities or measures for of these abilities may be more sensitive to global nonspecific deficits than are other abilities. The lack of controlling for symptoms it has to be also acknowledged. However, cognitive impairment is only modestly related to psychotic symptom severity and type (Harvey *et al.*, 1998, Nieuwenstein *et al.*, 2001, Tamminga *et al.*, 1998). Cognitive impairment appears to be a relatively independent aspect of schizophrenia. Impairment may be evident in a subtle form from early childhood, and often precedes the development of psychotic symptoms. Nonetheless although the follow up sample was representative, it may be that more severe patients were not included in the follow up study (or the opposite

## **Chapter 6 General discussion**

### **6.1 Introduction**

Neuropsychological impairments are central features in schizophrenia and are evident in overwhelming majority of patients. Although several studies have examined neuropsychological functioning in schizophrenia at first-onset, only a limited number of studies have investigated the course of illness and cognition over time. It is unclear for example, whether the level of neuropsychological dysfunction remains relatively static or whether for some patients at least, there is a progressive deterioration. Even less is known about neuropsychological functioning and clinical course in non-schizophrenic psychotic disorders. In this investigation I compared neuropsychological performance between patients experiencing their first psychotic episode in the context of four distinct diagnostic groups.

This thesis has the following specific aims:

- 1) Determine the neuropsychological profile at the first episode of psychosis
- 2) Examine if there are gender differences in the profile of neuropsychological performance
- 3) Determine the course of neuropsychological impairment over the first decade of illness.

Data comes from the AESOP (Aetiology and Ethnicity in Schizophrenia and Other Psychoses) study, a population based, case-control study of first episode psychosis. A comprehensive battery of neuropsychological tests was administered to patients and controls twice: at baseline (for patients – at their first admission), and follow-up (the mean time of follow-up was 104.2 months (SD=28.84)).

## **6.2 Summary of findings**

### **6.2.1 Neuropsychological profile at the first episode of psychosis**

The principle findings are that moderate to severe neuropsychological impairments characterize all psychotic disorders following the first psychotic episode, and that by-and-large, the magnitude of impairment on specific neuropsychological functions reflects a generalized cognitive deficit. Differences in neuropsychological performance between patient groups and controls, and between the different patient groups, were largely accounted for by differences in general intellectual ability. Only weak correlations were observed between neuropsychological functioning and symptom severity.

Despite the evidence that the neuropsychological impairment in psychotic disorders is generalized across the cognitive domains, additional specific deficits were also apparent. A selective deficit in working memory was evident in schizophrenic patients. In the depressive psychosis and other psychotic groups, a deficit beyond general intellectual impairment in verbal learning was evident. Finally, performance on the category (semantic) fluency test was selectively impaired, beyond general intellectual impairment, among patients with depressed psychosis and bipolar disorder or mania.

### **6.2.2 Gender differences in the profile of neuropsychological performance**

This investigation shows that gender differences in neuropsychological functions are disorder specific. Both males and females with schizophrenia showed similar pervasive neuropsychological impairments. Males with bipolar/manic or psychotic depressive disorders showed no significant impairments compared with healthy controls. There was also evidence of a gender based domain- specific impairment in bipolar/manic disorder. Females performed significantly worse than males on the language domain. Gender differences were not due to differences in symptom severity.

### **6.2.3 The course of neuropsychological impairment over the first decade of illness**

Findings from this study strongly support the hypotheses that schizophrenia is characterized by cognitive decline in generalised cognitive ability, especially verbal IQ. Cognitive decline appears to characterize verbal knowledge acquisition and also memory and reasoning abilities, yet to a lesser extent. A static impairment evident through adult life appears to characterise processing speed, visuospatial, language and executive function/working memory abilities.

Bipolar/Mania was also characterised by cognitive decline. Cognitive decline was evident in verbal knowledge acquisition. A static impairment evident through adult life appears to characterize processing speed, language and visuospatial abilities in bipolar/mania.

In depressive psychosis patients a static impairment was evident in general intellectual ability and on specific cognitive measures. Interestingly there was a frequent course of later-life amelioration for processing speed, executive function, language and learning and memory. In patients with other psychoses there was no evidence for decline in general intellectual ability. Memory functions including verbal and visual presented with a deteriorating course that began later in life. A course of amelioration appears to apply to processing speed.



### **6.3 Strengths and limitations of this investigation**

The present investigation has several strengths. First, it is a large, first-episode psychosis study incorporating a population-based epidemiological sample. A limitation of most previous studies is that they used clinical rather than epidemiological samples. Clinical samples involve patient series, not complete populations. As a result, it is difficult to generalize from studies using clinical samples. Second, this is an ethnically diverse sample. Third, this investigation includes a prospective follow-up component, following patients longitudinally after a first episode of psychosis. Previous studies of first-episode patients were well done and sometimes had large samples. However, studies varied considerably in terms of the sources for case ascertainment (e.g., university clinics, referral centres or in-patient samples), and the age, duration of illness and medication status of patients. Moreover, while some studies used specific diagnostic groups, others examined heterogeneous groups. These issues further hinder the interpretation of this research and the degree to which it can be generalised. The fact that a large healthy comparison group was included and similarly followed longitudinally also strengthens the interpretation of my results. Fourth, the diagnostic procedures were blind to neuropsychological assessment. Fifth, the longitudinal study used diagnoses at follow up and not baseline diagnoses. This was implemented to increase diagnostic reliability. Another strength of this investigation is the fact that the study examined six major domains of cognitive function known to be affected in schizophrenia: (1) Learning and Memory (verbal and visual); (2) Executive functions and working memory; (3) Attention, concentration and mental speed; (4) Language; (5) Visual constructual/perceptual abilities, and (6) verbal and non-verbal general intellectual ability (IQ) and therefore methodically evaluated the neuropsychological profile of impairment in psychotic patients.

Limitations of this investigation should, however, be acknowledged. One limitation is that no patients were drug naïve. Unfortunately I had insufficient information on medication to reliably determine dosage. Medication type or side effects could influence subjects' neuropsychological performance. However, it is an even more complex task to evaluate how the findings are affected by medication longitudinally when the doses of medication (antipsychotic, antidepressant, anticholinergic etc) might have changed dramatically or been discontinued. Nevertheless, only weak correlations between neuropsychological functioning and symptom severity were observed in the baseline study.

Most of the longitudinal studies are hampered by a certain dropout of patients and controls between the first and last assessments. Furthermore dropout to follow-up is a major source of information bias in studies whereby patients who are followed up differ systematically from those who are not followed up, or those followed for longer differ from those followed for less time. To reduce this type of bias I checked whether there were statistically significant differences between the subsamples of patients and controls that were followed up and the original cohort on measures of age, gender, ethnicity, education, IQ and premorbid IQ. I found that overall the patients from the original cohort at baseline were similar to those in the follow up in terms of the demographic variables. This similarity suggests that the follow up cohort is a representative sample of the original cohort at baseline.

In this investigation cases and controls were required to be native speakers of English or to have migrated to the UK by age 11. The latter requirement ensured that each participant had a good command of English as a non-native language as they would have completed at least their secondary education in the UK, thus minimising the effect of linguistic or cultural biases on the performance of a multi-ethnic sample. In accordance with previous studies (Reichenberg et al., 2008) cases or controls with missing data on more than three neuropsychological measures were excluded.

Another methodological shortcoming that should be pointed out concerns the practice or learning effects in test-retest. This shortcoming is usually controlled by including a comparison group of healthy participants screened for personal or family history of psychopathology. In this study, healthy controls were screened for the presence of psychotic symptoms with the Psychosis Screening Questionnaire (Bebbington and Nayani, 1995). However, with the long intervals between baseline and follow-up test assessments in the longitudinal studies, any carryover effect that occurs is probably minimal. This assumption is supported by the healthy control group data from Rund et al., (Rund *et al.*, 1993, 1997) longitudinal study.

## 6.4 Comparisons with other research

There is considerable variability in the profile and magnitude of cognitive impairment associated with psychosis. Even first episode patients that might represent the characteristics of schizophrenia more definitely have variation in the extent of impairment across neuropsychological domains (Kravariti *et al.*, 2009). Some show impairment in only a few domains relative to healthy control participants, while others show a range of deficits in most or all domains. My results concord with the majority of studies (Addington *et al.*, 2003, Albus *et al.*, 1996, Goldberg *et al.*, 1993, Hoff *et al.*, 1992, Jeste *et al.*, 1996, Krabbendam *et al.*, 2005, Mohamed *et al.*, 1999, Riley *et al.*, 2000, Saykin *et al.*, 1991) by showing that in early course of illness, cognitive impairment is present in all psychotic disorders but is most severe and pervasive in schizophrenia and least pervasive in bipolar and mania.

Although there is wide acceptance that schizophrenia is accompanied by a cognitive impairment, there is no consensus on the precise course of the neuropsychological impairment. Rund (Rund, 1998) in his review of longitudinal studies of cognitive functions in schizophrenia concluded that schizophrenia appears to be a static encephalopathy. After reviewing 15 follow-up studies he reported stability of cognition and no evidence of a decline, which confirms the neurodevelopmental view of the disorder as opposed to degeneration in schizophrenia. This stability mainly refers to verbal skills, memory and pre-attentive information processing. Moreover Bozikas and Andreou (Bozikas and Andreou, 2011) in their review of longitudinal studies of cognitive functions in first episode of psychosis summed up that the cognitive deficits that are present at first episode of psychosis appeared to remain stable over time for periods of up to ten years, with a possible exception being verbal memory deficits where there is some evidence of further deterioration over the long time period. Longitudinally, the present findings add to the evidence that in multiple cognitive domains neuropsychological impairment is already present at the onset of illness and persists throughout adult life. Nevertheless, change, and in particular decline does occur, and was evident in general intellectual ability and verbal memory in schizophrenia. This is in concordance with studies by Hoff *et al.*, where some neuropsychological functions were found to deteriorate over long time periods (Hoff *et al.*, 1999, Hoff *et al.*, 2005). The most stable cognitive domains appear to be executive function, language and sensory/perceptual abilities. The findings are consistent with reports in the literature (Bozikas and

Andreou, 2011). Whether this heterogeneity of cognitive impairment reflects specific brain dysfunctions within distinct genetic subtypes or individual variation in the effects of a general underlying pathophysiology is still not understood (Dickinson and Harvey, 2009).

It is now widely accepted that cognitive abnormalities are a key feature of bipolar disorder (Arts *et al.*, 2008, Bora *et al.*, 2009, Kumar and Frangou, 2010). However, cognitive dysfunction in patients with bipolar disorder has been reported predominantly in chronic patients during acute episodes (Quraishi and Frangou, 2002). It is unclear whether cognitive impairments are present at illness onset. Previous studies, typically with chronic patients, have reported more severe impairments in schizophrenia compared to affective disorders, but qualitatively similar cognitive profiles (Albus *et al.*, 1996, Reichenberg *et al.*, 2010), particularly for psychotic affective disorders (Jeste *et al.*, 1996, Mojtabai *et al.*, 2000). Mojtabai *et al.*, (Mojtabai *et al.*, 2000) reported that first episode bipolar disorder patients performed better than schizophrenic patients in all subscales of the WMS, especially in the subtest of delayed visual short term memory. In the present study a considerable overlap was found between the patients with schizophrenia and bipolar/mania in terms of neuropsychological impairment, nevertheless, bipolar patients showed less severe decrements in performance.

Studies investigating the stability of cognitive impairment in bipolar/mania patients are rare and available data with chronic bipolar disorder (Balanza-Martinez *et al.*, 2005) suggest persistent deficits. There is evidence that certain cognitive dysfunctions are stable over time (Balanza-Martinez *et al.*, 2005, Mur *et al.*, 2008) and persist during euthymia, as shown in several recent meta-analyses (Arts *et al.*, 2008, Bora *et al.*, 2009). Embedding my findings with previous research, it is highly likely that as proposed in schizophrenia, cognitive deficits arise from neurodevelopmental and neurodegenerative origin. An important distinction between schizophrenia and bipolar/mania, is nonetheless, the presence of continuously preserved functions in bipolar disorder, such as executive function and working memory.

Although gender differences have been reported on neuropsychological testing, the nature of these differences is controversial. In this investigation there were no statistically significant differences in neuropsychological functioning between males and females with schizophrenia or schizoaffective disorder. Differences in neuropsychological performance between males and females with bipolar/manic disorder were restricted to language functions. In psychotic depressive disorder females performed worse than males across neuropsychological measures.

Some studies show that schizophrenic males have more cognitive deficits (especially in verbal processing) others show females perform worse or do not show any differences in neuropsychological test performance between the sexes. The findings of this investigation are consistent with studies reporting lack of gender differences in cognitive performance between schizophrenic patients and controls (Andia *et al.*, 1995, Goldberg *et al.*, 1995, Haas *et al.*, 1991, Hoff *et al.*, 1998). These inconsistencies in the results of studies examining gender and cognition in schizophrenia demonstrate many of the difficulties encountered in studies of gender and schizophrenia in general. Goldstein (Goldstein, 1996b) and Seidman *et al.* (Seidman *et al.*, 1997) have suggested that samples of convenience may not include representative male and female patients, i.e. sex differences may not emerge if the sample consists of males and females who express a similar sub-type of schizophrenia. Furthermore, the specific functions assessed may not be the ones on which male and female differ on (Seidman *et al.*, 1997). Hoff *et al.* (Hoff *et al.*, 1998) proposed that gender differences in cognitive performance may be due to gender differences in age of onset or illness severity, and if these variables are controlled, gender differences in cognitive performance may be insignificant. However, controlling for age of onset and severity of illness may lead to non representative sampling of the population of schizophrenic males and females as a whole. Other methodological concerns include lack of within gender normal comparison groups, inadequate sample sizes to test for gender effects (as group differences generally exceed more subtle gender differences) and sampling of acutely ill patients (reflecting state rather than trait effects) (Goldstein *et al.*, 1998, Hoff *et al.*, 1998). Goldstein *et al.* (Goldstein *et al.*, 1998) noted the vast majority of studies do not match schizophrenic patients with normal subjects within gender. Although there are significant gender differences in cognition in the normal population, these gender effect sizes are small, and because within gender variability is greater than between gender variability in normal subjects, having within gender comparison

groups increases the statistical power to detect gender differences in schizophrenic patients. Haas et al. (Haas *et al.*, 1991) failed to find gender differences in cognitive impairment of first episode patients, but in patients who had been ill for 5 years or longer, males showed greater deficits on verbal tasks, indicative of left hemisphere dysfunction. It becomes clear that gender differences in cognitive function in patients with schizophrenia are not robust findings. At present there is no generally agreed neuropsychological profile *per se* of male and female schizophrenic patients. Whether a distinctive pattern of neuropsychological dysfunction in males and females exist it remains to be determined.

Only of studies addressed directly the issue of gender differences in cognition in bipolar disorder. Barrett et al. (Barrett *et al.*, 2008) Male patients performed worse than female patients in measures of spatial working memory, indicative of poor retention of visuospatial information. However, male patients in this study were both older and more symptomatic than female patients. Carrus et al., found a gender effect and an interaction between diagnosis and gender on immediate memory, implicating encoding and retrieval processes, both showing male bipolar disorder patients being disadvantaged compared with female patients and healthy controls (Carrus *et al.*, 2010). The potential effect of gender was also explored in the meta-analysis by Arts et al., who reported smaller effect sizes for concept formation and perseveration in studies with higher male to female ratios (Arts *et al.*, 2008). Although the existing evidence regarding gender effects on neuropsychological function in bipolar disorder is both incomplete and contradictory, the results of my investigation support the notion that gender related factors appear to moderate the severity of cognitive deficits in bipolar/mania.

To my knowledge so far no study exists to address directly the issue of gender differences in cognition in depressive psychosis and other psychotic disorders. Further research is needed.

## 6.5 Integration of findings

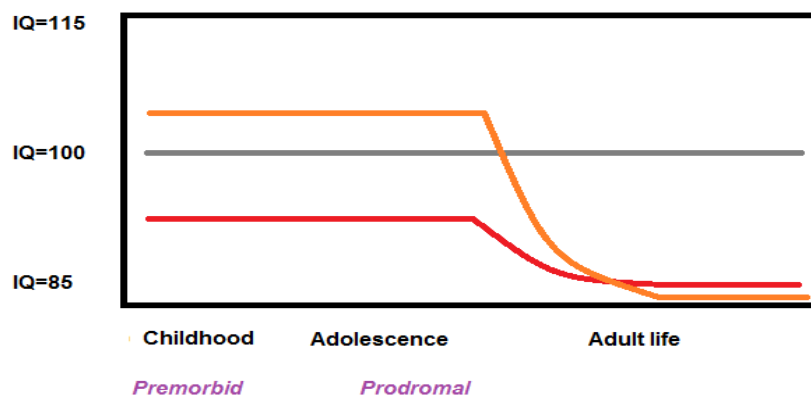
Despite increasing evidence of cognitive dysfunction in patients with schizophrenia and in patients with affective disorders, few studies have directly compared the groups longitudinally. There is robust evidence that cognitive deficits exist early in course of the illness in schizophrenia while such deficits are either nonexistent or mild in first episode of bipolar disorder (Gilvarry *et al.*, 2001, Krabbendam *et al.*, 2005, Zanelli *et al.*, 2010). It is estimated that neuropsychological performance in schizophrenia patients range from one to two standard deviations below that of healthy comparison controls (Bilder *et al.*, 2000, Woodberry *et al.*, 2008). Birth cohort studies consistently indicate that patients with schizophrenia have premorbid cognitive impairments. These deficits appear absent or even reversed (i.e., superior performance) in children who will later develop bipolar disorder. Cannon *et al.*, reported that preschizophreniform children showed deficits in cognitive function and neuromotor development but children who went on to develop mania by 26 years performed significantly better than controls on motor performance (Cannon *et al.*, 2002a). A consequential analysis of data from the 32-year follow-up showed that higher childhood IQ predicted risk of later mania (Koenen *et al.*, 2009).

Integrating results from studies of premorbid functioning and current study I proposed the following model to describe the life course of the cognitive function in schizophrenia and bipolar/mania disorder. This was developed based on the available literature on premorbid cognitive functioning and the current findings (Cannon *et al.*, 2002a, Cannon *et al.*, 2000, Reichenberg *et al.*, 2010).

Future schizophrenia patients show impairments in general intellectual ability (IQ) early in development. This impairment remains static with a magnitude of about half a standard deviation (7 IQ points) until late adolescence (Reichenberg *et al.*, 2010). Combining previous research on premorbid functioning and the current study results suggest that the IQ deficit increases in magnitude starting in late adolescence or early adult life (**Figure 6.1**). This increase in the magnitude of impairment is predominantly in measures relying on knowledge acquisition, and is reflected by increasingly greater deficits in verbal IQ. The impairment in performance IQ does not seem to further increase after late adolescence/early adult life. Bipolar patients present with

normal, or even superior IQ in childhood (Koenen *et al.*, 2009) and also adolescence (Dunedin study, unpublished data, Reichenberg – Personal communication and (MacCabe *et al.*, 2010)). As in schizophrenia verbal IQ begins to deteriorate in late adolescence or early adult life, and the resulting impairment is as severe as the one seen in schizophrenia (**Figure 6.1**).

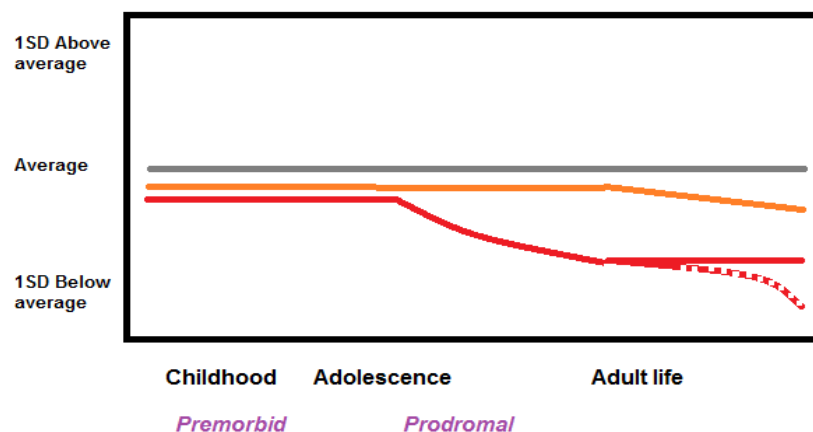
**Figure 6.1** The life course trajectory of cognitive impairment in schizophrenia and bipolar/mania – general intellectual abilities. (Red line represents schizophrenia patients; Orange line represents bipolar/mania patients; Gray line represents controls).





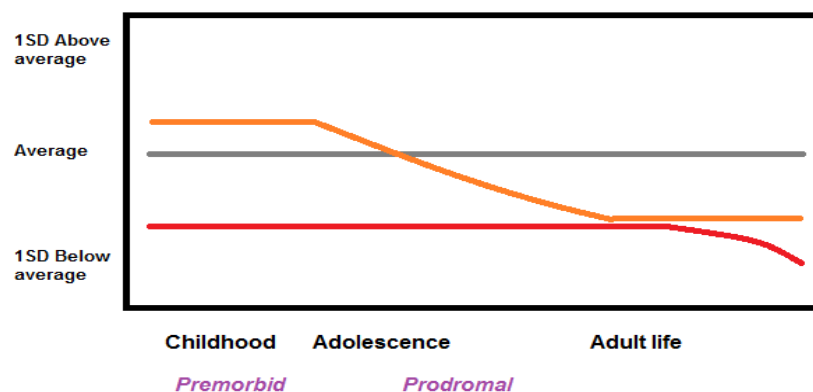
Figures 6.2 – 6.5 present the life course trajectories of cognitive functioning in schizophrenia and bipolar disorder on specific neuropsychological domains: Memory, language, working memory and executive functions and processing speed. Both schizophrenia and bipolar/mania show intact memory functions in childhood and adolescence. (**Figure 6.2**). Memory functions begin to deteriorate in schizophrenia in late adolescence/early adult life, a processes which possibly continuous throughout their adult life, at least for some specific functions. In contrast, patients with bipolar/mania show intact memory functions until late in adult life (**Figure 6.2**).

**Figure 6.2 The life course trajectory of cognitive impairment in schizophrenia and bipolar/mania – memory. (Red line represents schizophrenia patients; Orange line represents bipolar/mania patients; Gray line represents controls).**



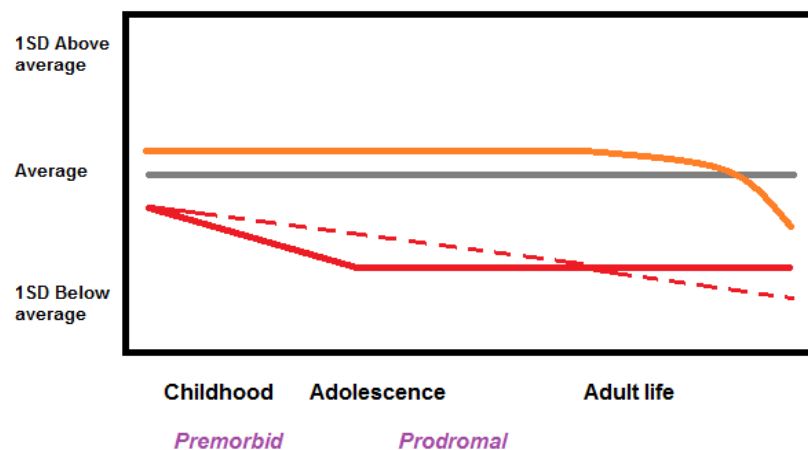
Future schizophrenia patients exhibit impairments on language abilities which are already present in childhood (**Figure 6.3**). In contrast, patients with bipolar/mania show normal or even superior language abilities in childhood which then begin to deteriorate. This process continues until early adult life and remains static thereafter. (**Figure 6.3**).

**Figure 6.3** The life course trajectory of cognitive impairment in schizophrenia and bipolar/mania – language. (Red line represents schizophrenia patients; Orange line represents bipolar/mania patients; Gray line represents controls).



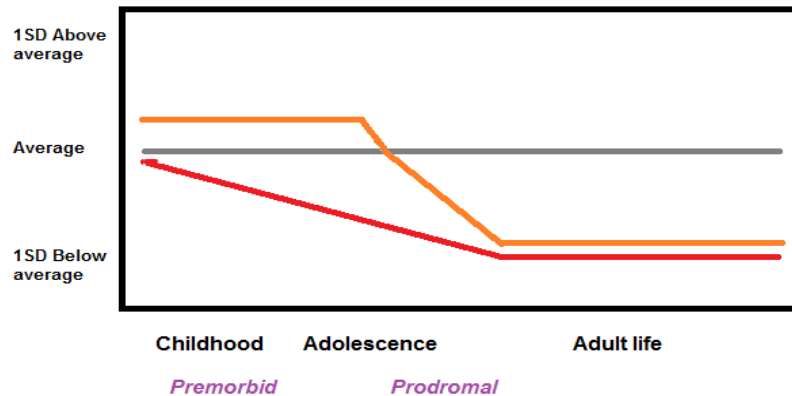
On cognitive tests assessing working memory and executive function, future schizophrenia patients are impaired early in development. This impairment becomes static after adolescence or early adult life (**Figure 6.4**). In bipolar/mania, there is no impairment in working memory and executive function but there might be some decline on these functions later in life (**Figure 6.4**)

**Figure 6.4** The life course trajectory of cognitive impairment in schizophrenia and bipolar/mania – working memory and executive function. (Red line represents schizophrenia patients; Orange line represents bipolar/mania patients; Gray line represents controls).



In case of processing speed, it appears that future schizophrenia patients begin to decline from childhood and continue to decline until adulthood. This impairment does not seem to further increase in magnitude and remains static throughout adult life (**Figure 6.5**). However, bipolar/mania patients are unimpaired in childhood but seem to decline from early adolescence until adulthood. Thereafter this impairment is static as in schizophrenia patients (**Figure 6.5**).

**Figure 6.5 The life course trajectory of cognitive impairment in schizophrenia and bipolar/mania – processing speed. (Red line represents schizophrenia patients; Orange line represents bipolar/mania patients; Gray line represents controls).**



Thus, both schizophrenia and bipolar/mania patients show dynamic changes in general and specific cognitive functions which start early in childhood and continue across the life span.

Recently developmental studies in psychiatry are shifting from exploring risk factors (e.g., from studying whether low IQ predicts onset of psychotic illness) to examining models that can essay age-related changes in brain function. Although individuals with schizophrenia and individuals with bipolar/mania share multiple cognitive impairments, the findings from this study show a clear distinction between schizophrenia and bipolar/mania in the life course trajectory of cognitive impairment. Future research should explore the pathogenic mechanisms underlying the different trajectory of cognitive impairment.

The findings should be interpreted in light of some limitations. The literature in mania argues that the number of episodes predicts the cognitive impairment. However, there was no reliable data on number and duration of manic episodes. Both depressive psychosis and other psychotic disorders show different age related changes than schizophrenia or bipolar/mania. However because of small sample size and lack of studies examining the premorbid period therefore it is difficult to provide a life course model. Nonetheless, intriguing findings suggest that future studies are needed.

## 6.6 Future directions

Additional studies are needed to investigate the impact of gender differences on cognitive deficits across psychotic disorders. If future research should conclusively establish progressive neuropsychological decline in a subset of schizophrenic patients, question arise as to why only a minority are so affected. Is this another example of the heterogeneous manifestations of a common disease (Andreasen, 1999, Palmer *et al.*, 1999) or other factors are involved, for example treatment history or comorbid conditions.

Future research should aim to understand the pathogenic mechanisms underlying the different courses of cognitive deficits in psychotic patients. Also the time pattern of cognitive decline over life needs to be further explored. Those cognitive deficits that are fixed and those that are most sensitive to change have to be indentified in order to facilitate the assessment of interventions, pharmacological treatments and/or cognitive rehabilitation programmes, aiming at the improvements of cognitive functions

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